Welcome to STN International! Enter x:x

LOGINID:ssspta1600rxa

PASSWORD:
TERMINAL (ENTER 1, 2, 3, OR ?):2

* * * * * * * * * * Welcome to STN International * * * * * * * * * *

NEWS 1		Web Page URLs for STN Seminar Schedule - N. America
NEWS 2		"Ask CAS" for self-help around the clock
NEWS 3	Jun 03	New e-mail delivery for search results now available
NEWS 4	Aug 08	PHARMAMarketLetter(PHARMAML) - new on STN
NEWS 5	Aug 19	Aquatic Toxicity Information Retrieval (AQUIRE) now available on STN
NEWS 6	Aug 26	Sequence searching in REGISTRY enhanced
NEWS 7	Sep 03	JAPIO has been reloaded and enhanced
NEWS 8	Sep 16	Experimental properties added to the REGISTRY file
NEWS 9	Sep 16	CA Section Thesaurus available in CAPLUS and CA
NEWS 10	Oct 01	CASREACT Enriched with Reactions from 1907 to 1985
NEWS 11	Oct 24	BEILSTEIN adds new search fields
NEWS 12	Oct 24	Nutraceuticals International (NUTRACEUT) now available on STN
NEWS 13	Nov 18	DKILIT has been renamed APOLLIT
NEWS 14	Nov 25	More calculated properties added to REGISTRY
NEWS 15	Dec 04	CSA files on STN
NEWS 16	Dec 17	PCTFULL now covers WP/PCT Applications from 1978 to date
NEWS 17	Dec 17	TOXCENTER enhanced with additional content
NEWS 18	Dec 17	Adis Clinical Trials Insight now available on STN
NEWS 19	Jan 29	Simultaneous left and right truncation added to COMPENDEX, ENERGY, INSPEC
NEWS 20	Feb 13	CANCERLIT is no longer being updated
NEWS 21	Feb 24	METADEX enhancements
NEWS 22	Feb 24	PCTGEN now available on STN
NEWS 23	Feb 24	TEMA now available on STN
NEWS 24	Feb 26	NTIS now allows simultaneous left and right truncation
NEWS 25	Feb 26	PCTFULL now contains images
NEWS 26	Mar 04	SDI PACKAGE for monthly delivery of multifile SDI results
NEWS 27	Mar 20	EVENTLINE will be removed from STN
NEWS 28	Mar 24	PATDPAFULL now available on STN
NEWS 29	Mar 24	Additional information for trade-named substances without structures available in REGISTRY
NEWS 30	Apr 11	Display formats in DGENE enhanced
NEWS 31	Apr 14	MEDLINE Reload
NEWS 32	Apr 17	Polymer searching in REGISTRY enhanced
NEWS 33	Jun 13	Indexing from 1947 to 1956 added to records in CA/CAPLUS
NEWS 34	Apr 21	New current-awareness alert (SDI) frequency in WPIDS/WPINDEX/WPIX
NEWS 35	Apr 28	RDISCLOSURE now available on STN
NEWS 36	May 05	Pharmacokinetic information and systematic chemical names added to PHAR
NEWS 37	May 15	MEDLINE file segment of TOXCENTER reloaded
NEWS 38	May 15	Supporter information for ENCOMPPAT and ENCOMPLIT updated
NEWS 39	May 16	CHEMREACT will be removed from STN
NEWS 40	May 19	Simultaneous left and right truncation added to WSCA
NEWS 41	May 19	RAPRA enhanced with new search field, simultaneous left and right truncation
NEWS 42	Jun 06	Simultaneous left and right truncation added to CBNB
NEWS 43	Jun 06	PASCAL enhanced with additional data

```
 NEWS EXPRESS  April 4 CURRENT WINDOWS VERSION IS V6.01a, CURRENT
               MACINTOSH VERSION IS V6.0b(ENG) AND V6.0Jb(JP),
               AND CURRENT DISCOVER FILE IS DATED 01 APRIL 2003
 NEWS HOURS    STN Operating Hours Plus Help Desk Availability
 NEWS INTER    General Internet Information
 NEWS LOGIN    Welcome Banner and News Items
 NEWS PHONE    Direct Dial and Telecommunication Network Access to STN
 NEWS WWW      CAS World Wide Web Site (general information)

Enter NEWS followed by the item number or name to see news on that
specific topic.

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  result in loss of user privileges and other penalties.

  * * * * * * * * * * * * * * STN  Columbus  * * * * * * * * * * * * * * *

FILE 'HOME' ENTERED AT 08:08:22 ON 19 JUN 2003

=> fil reg
COST IN U.S. DOLLARS                                SINCE FILE      TOTAL
                                                       ENTRY    SESSION
FULL ESTIMATED COST                                     0.21       0.21

FILE 'REGISTRY' ENTERED AT 08:08:33 ON 19 JUN 2003
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Property values tagged with IC are from the ZIC/VINITI data file
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STRUCTURE FILE UPDATES:   17 JUN 2003  HIGHEST RN 532924-24-6
DICTIONARY FILE UPDATES:  17 JUN 2003  HIGHEST RN 532924-24-6

TSCA INFORMATION NOW CURRENT THROUGH JANUARY 6, 2003

  Please note that search-term pricing does apply when
  conducting SmartSELECT searches.

Crossover limits have been increased.  See HELP CROSSOVER for details.

Experimental and calculated property data are now available.  See HELP
PROPERTIES for more information.  See STNote 27, Searching Properties
in the CAS Registry File, for complete details:
http://www.cas.org/ONLINE/STN/STNOTES/stnotes27.pdf

=>
Uploading 10049248.str

L1      STRUCTURE UPLOADED

=> d
L1 HAS NO ANSWERS
L1              STR
```

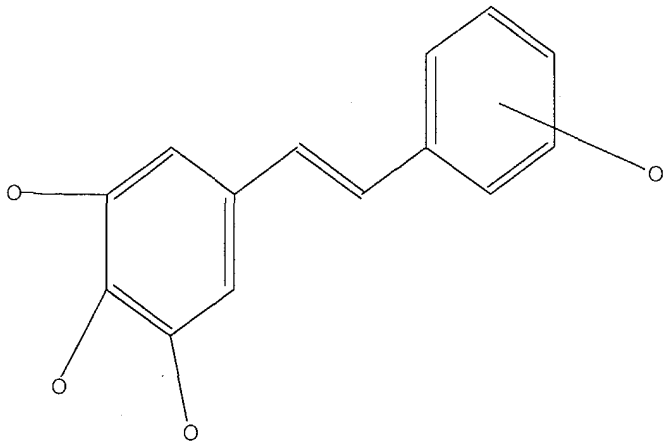

Structure attributes must be viewed using STN Express query preparation.

```
=> s l1
SAMPLE SEARCH INITIATED 08:08:48 FILE 'REGISTRY'
SAMPLE SCREEN SEARCH COMPLETED -    133 TO ITERATE

100.0% PROCESSED     133 ITERATIONS                          41 ANSWERS
SEARCH TIME: 00.00.01

FULL FILE PROJECTIONS:  ONLINE  **COMPLETE**
                        BATCH   **COMPLETE**
PROJECTED ITERATIONS:         1969 TO     3351
PROJECTED ANSWERS:             435 TO     1203

L2            41 SEA SSS SAM L1

=> s l1 full
FULL SEARCH INITIATED 08:08:52 FILE 'REGISTRY'
FULL SCREEN SEARCH COMPLETED -   2301 TO ITERATE

100.0% PROCESSED    2301 ITERATIONS                         675 ANSWERS
SEARCH TIME: 00.00.01

L3           675 SEA SSS FUL L1

=> fil caplus
COST IN U.S. DOLLARS                          SINCE FILE      TOTAL
                                                 ENTRY    SESSION
FULL ESTIMATED COST                             148.15     148.36

FILE 'CAPLUS' ENTERED AT 08:08:54 ON 19 JUN 2003
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```

FILE COVERS 1907 - 19 Jun 2003 VOL 138 ISS 25
FILE LAST UPDATED: 18 Jun 2003 (20030618/ED)

This file contains CAS Registry Numbers for easy and accurate substance identification.

=> s l3
L4 407 L3

=> fil reg

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	0.42	148.78

FILE 'REGISTRY' ENTERED AT 08:09:00 ON 19 JUN 2003

Property values tagged with IC are from the ZIC/VINITI data file provided by InfoChem.

STRUCTURE FILE UPDATES: 17 JUN 2003 HIGHEST RN 532924-24-6
DICTIONARY FILE UPDATES: 17 JUN 2003 HIGHEST RN 532924-24-6

TSCA INFORMATION NOW CURRENT THROUGH JANUARY 6, 2003

Please note that search-term pricing does apply when conducting SmartSELECT searches.

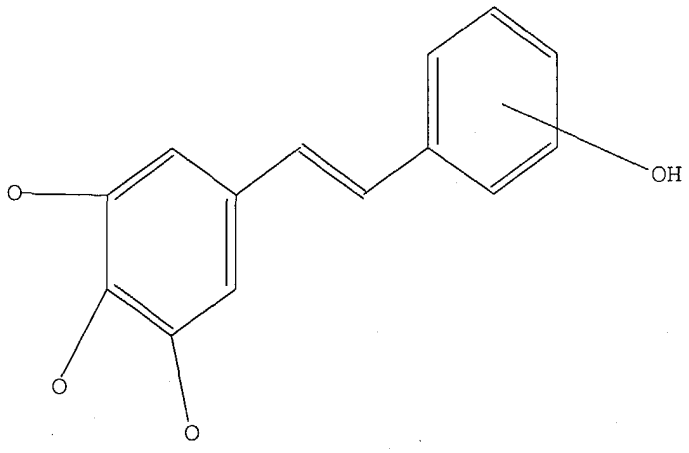
Crossover limits have been increased. See HELP CROSSOVER for details.

Experimental and calculated property data are now available. See HELP PROPERTIES for more information. See STNote 27, Searching Properties in the CAS Registry File, for complete details:
http://www.cas.org/ONLINE/STN/STNOTES/stnotes27.pdf

=>
Uploading 10049248.str

L5 STRUCTURE UPLOADED

=> d
L5 HAS NO ANSWERS
L5 STR



Structure attributes must be viewed using STN Express query preparation.

```
=> d his

     (FILE 'HOME' ENTERED AT 08:08:22 ON 19 JUN 2003)

     FILE 'REGISTRY' ENTERED AT 08:08:33 ON 19 JUN 2003
L1             STRUCTURE UPLOADED
L2              41 S L1
L3             675 S L1 FULL

     FILE 'CAPLUS' ENTERED AT 08:08:54 ON 19 JUN 2003
L4             407 S L3

     FILE 'REGISTRY' ENTERED AT 08:09:00 ON 19 JUN 2003
L5             STRUCTURE UPLOADED

=> s l5 subset=l3 full
FULL SUBSET SEARCH INITIATED 08:09:42 FILE 'REGISTRY'
FULL SUBSET SCREEN SEARCH COMPLETED -     675 TO ITERATE

100.0% PROCESSED     675 ITERATIONS                          108 ANSWERS
SEARCH TIME: 00.00.01

L6             108 SEA SUB=L3 SSS FUL L5

=> fil caplus
COST IN U.S. DOLLARS                          SINCE FILE      TOTAL
                                                   ENTRY    SESSION
FULL ESTIMATED COST                               35.30     184.08

FILE 'CAPLUS' ENTERED AT 08:09:44 ON 19 JUN 2003
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FILE COVERS 1907 - 19 Jun 2003 VOL 138 ISS 25
FILE LAST UPDATED: 18 Jun 2003 (20030618/ED)

This file contains CAS Registry Numbers for easy and accurate substance identification.

=> s l6
L7 218 L6

=> fil reg

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	0.42	184.50

FILE 'REGISTRY' ENTERED AT 08:09:51 ON 19 JUN 2003
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Property values tagged with IC are from the ZIC/VINITI data file provided by InfoChem.

STRUCTURE FILE UPDATES: 17 JUN 2003 HIGHEST RN 532924-24-6
DICTIONARY FILE UPDATES: 17 JUN 2003 HIGHEST RN 532924-24-6

TSCA INFORMATION NOW CURRENT THROUGH JANUARY 6, 2003

Please note that search-term pricing does apply when conducting SmartSELECT searches.

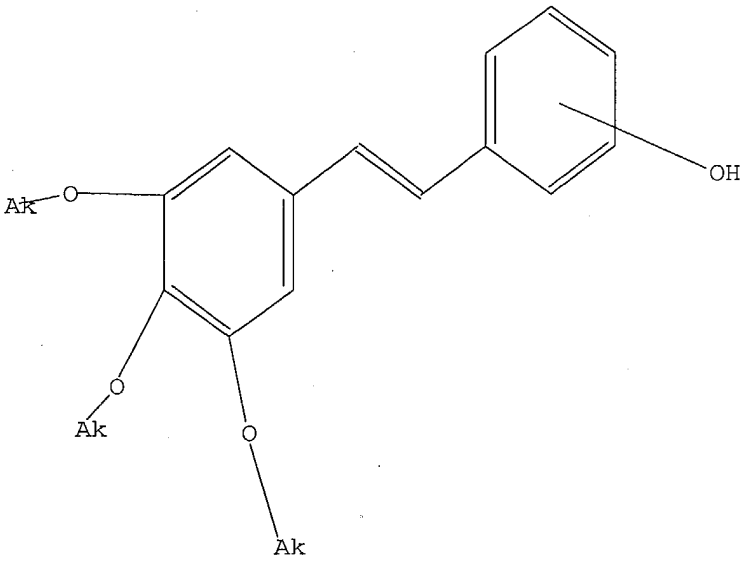
Crossover limits have been increased. See HELP CROSSOVER for details.

Experimental and calculated property data are now available. See HELP PROPERTIES for more information. See STNote 27, Searching Properties in the CAS Registry File, for complete details:
http://www.cas.org/ONLINE/STN/STNOTES/stnotes27.pdf

=>
Uploading 10049248.str

L8 STRUCTURE UPLOADED

=> d
L8 HAS NO ANSWERS
L8 STR



Structure attributes must be viewed using STN Express query preparation.

=> s l8 subset=l6 full
FULL SUBSET SEARCH INITIATED 08:10:32 FILE 'REGISTRY'
FULL SUBSET SCREEN SEARCH COMPLETED - 108 TO ITERATE

100.0% PROCESSED 108 ITERATIONS 76 ANSWERS
SEARCH TIME: 00.00.01

L9 76 SEA SUB=L6 SSS FUL L8

=> fil caplus

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	35.30	219.80

FILE 'CAPLUS' ENTERED AT 08:10:35 ON 19 JUN 2003
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.

FILE COVERS 1907 - 19 Jun 2003 VOL 138 ISS 25
FILE LAST UPDATED: 18 Jun 2003 (20030618/ED)

This file contains CAS Registry Numbers for easy and accurate

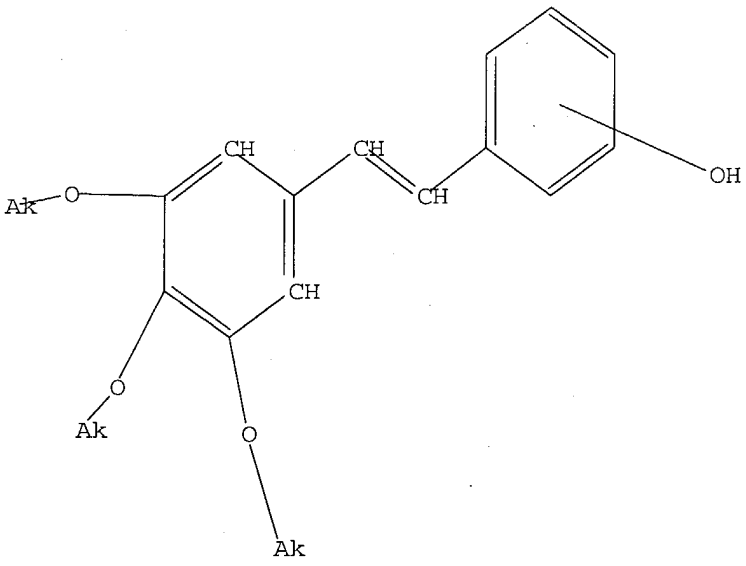
substance identification.

=> s l9
L10 169 L9

=>
Uploading 10049248.str

L11 STRUCTURE UPLOADED

=> d
L11 HAS NO ANSWERS
L11 STR



Structure attributes must be viewed using STN Express query preparation.

=> s l11 subset=l9 full
REG1stRY INITIATED
Substance data SEARCH and crossover from CAS REGISTRY in progress...
Use DISPLAY HITSTR (or FHITSTR) to directly view retrieved structures.

FULL SUBSET SEARCH INITIATED 08:11:31 FILE 'REGISTRY'
FULL SUBSET SCREEN SEARCH COMPLETED - 76 TO ITERATE

100.0% PROCESSED 76 ITERATIONS 60 ANSWERS
SEARCH TIME: 00.00.01

L12 60 SEA SUB=L9 SSS FUL L11

SUBSET IS IGNORED AS A SCOPE FOR THIS SEARCH

L13 166 L12

=> fil reg

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	0.42	256.35

FILE 'REGISTRY' ENTERED AT 08:11:35 ON 19 JUN 2003
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PLEASE SEE "HELP USAGETERMS" FOR DETAILS.

Property values tagged with IC are from the ZIC/VINITI data file provided by InfoChem.

STRUCTURE FILE UPDATES: 17 JUN 2003 HIGHEST RN 532924-24-6
DICTIONARY FILE UPDATES: 17 JUN 2003 HIGHEST RN 532924-24-6

TSCA INFORMATION NOW CURRENT THROUGH JANUARY 6, 2003

Please note that search-term pricing does apply when conducting SmartSELECT searches.

Crossover limits have been increased. See HELP CROSSOVER for details.

Experimental and calculated property data are now available. See HELP PROPERTIES for more information. See STNote 27, Searching Properties in the CAS Registry File, for complete details:
http://www.cas.org/ONLINE/STN/STNOTES/stnotes27.pdf

=> s l11 subset=l9 full
FULL SUBSET SEARCH INITIATED 08:11:41 FILE 'REGISTRY'
FULL SUBSET SCREEN SEARCH COMPLETED - 76 TO ITERATE

100.0% PROCESSED 76 ITERATIONS 60 ANSWERS
SEARCH TIME: 00.00.01

L14 60 SEA SUB=L9 SSS FUL L11

=> fil caplus

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	35.30	291.65

FILE 'CAPLUS' ENTERED AT 08:11:44 ON 19 JUN 2003
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FILE COVERS 1907 - 19 Jun 2003 VOL 138 ISS 25
FILE LAST UPDATED: 18 Jun 2003 (20030618/ED)

This file contains CAS Registry Numbers for easy and accurate substance identification.

```
=> s l14
L15         166 L14

=> fil reg
COST IN U.S. DOLLARS                                  SINCE FILE      TOTAL
                                                         ENTRY    SESSION
FULL ESTIMATED COST                                       0.42     292.07

FILE 'REGISTRY' ENTERED AT 08:12:16 ON 19 JUN 2003
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STRUCTURE FILE UPDATES:   17 JUN 2003  HIGHEST RN 532924-24-6
DICTIONARY FILE UPDATES:  17 JUN 2003  HIGHEST RN 532924-24-6

TSCA INFORMATION NOW CURRENT THROUGH JANUARY 6, 2003
```

Please note that search-term pricing does apply when conducting SmartSELECT searches.

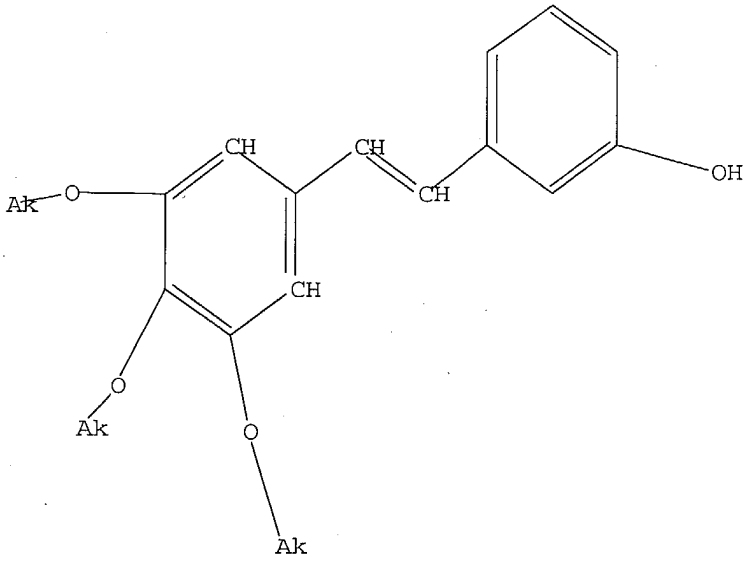
```
Crossover limits have been increased.  See HELP CROSSOVER for details.

Experimental and calculated property data are now available.  See HELP
PROPERTIES for more information.  See STNote 27, Searching Properties
in the CAS Registry File, for complete details:
http://www.cas.org/ONLINE/STN/STNOTES/stnotes27.pdf

=>
Uploading 10049248.str

L16      STRUCTURE UPLOADED

=> d
L16 HAS NO ANSWERS
L16              STR
```



Structure attributes must be viewed using STN Express query preparation.

```
=> s l16 subset=l14 full
FULL SUBSET SEARCH INITIATED 08:12:32 FILE 'REGISTRY'
FULL SUBSET SCREEN SEARCH COMPLETED -      60 TO ITERATE

100.0% PROCESSED      60 ITERATIONS                              46 ANSWERS
SEARCH TIME: 00.00.01

L17           46 SEA SUB=L14 SSS FUL L16

=> fil caplus
COST IN U.S. DOLLARS                                SINCE FILE      TOTAL
                                                       ENTRY    SESSION
FULL ESTIMATED COST                                    35.30     327.37

FILE 'CAPLUS' ENTERED AT 08:12:34 ON 19 JUN 2003
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FILE COVERS 1907 - 19 Jun 2003  VOL 138 ISS 25
FILE LAST UPDATED: 18 Jun 2003  (20030618/ED)
```

This file contains CAS Registry Numbers for easy and accurate

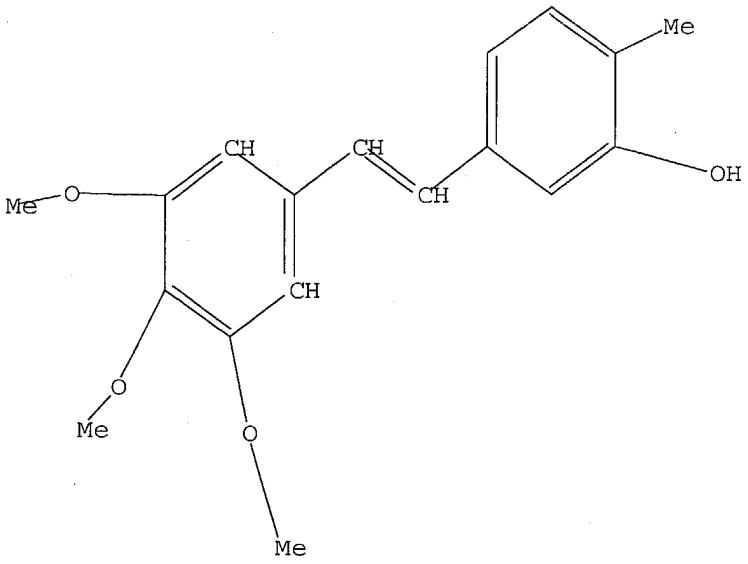
substance identification.

```
=> s l17
L18         160 L17

=>
Uploading 10049248.str

L19      STRUCTURE UPLOADED

=> d
L19 HAS NO ANSWERS
L19              STR
```



Structure attributes must be viewed using STN Express query preparation.

```
=> fil reg
COST IN U.S. DOLLARS                                  SINCE FILE      TOTAL
                                                         ENTRY    SESSION
FULL ESTIMATED COST                                       0.83     328.20

FILE 'REGISTRY' ENTERED AT 08:13:32 ON 19 JUN 2003
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STRUCTURE FILE UPDATES:   17 JUN 2003  HIGHEST RN 532924-24-6
DICTIONARY FILE UPDATES:  17 JUN 2003  HIGHEST RN 532924-24-6

TSCA INFORMATION NOW CURRENT THROUGH JANUARY 6, 2003

  Please note that search-term pricing does apply when
  conducting SmartSELECT searches.
```

Crossover limits have been increased. See HELP CROSSOVER for details.

Experimental and calculated property data are now available. See HELP PROPERTIES for more information. See STNote 27, Searching Properties in the CAS Registry File, for complete details:
http://www.cas.org/ONLINE/STN/STNOTES/stnotes27.pdf

=> d his

(FILE 'HOME' ENTERED AT 08:08:22 ON 19 JUN 2003)

FILE 'REGISTRY' ENTERED AT 08:08:33 ON 19 JUN 2003
L1 STRUCTURE UPLOADED
L2 41 S L1
L3 675 S L1 FULL

FILE 'CAPLUS' ENTERED AT 08:08:54 ON 19 JUN 2003
L4 407 S L3

FILE 'REGISTRY' ENTERED AT 08:09:00 ON 19 JUN 2003
L5 STRUCTURE UPLOADED
L6 108 S L5 FULL SUB=L3

FILE 'CAPLUS' ENTERED AT 08:09:44 ON 19 JUN 2003
L7 218 S L6

FILE 'REGISTRY' ENTERED AT 08:09:51 ON 19 JUN 2003
L8 STRUCTURE UPLOADED
L9 76 S L8 FULL SUB=L6

FILE 'CAPLUS' ENTERED AT 08:10:35 ON 19 JUN 2003
L10 169 S L9
L11 STRUCTURE UPLOADED
S L11

FILE 'REGISTRY' ENTERED AT 08:11:31 ON 19 JUN 2003
L12 60 S L11 FULL SUB=L9

FILE 'CAPLUS' ENTERED AT 08:11:32 ON 19 JUN 2003
L13 166 S L12 SUBSET=L9 FULL

FILE 'REGISTRY' ENTERED AT 08:11:35 ON 19 JUN 2003
L14 60 S L11 FULL SUB=L9

FILE 'CAPLUS' ENTERED AT 08:11:44 ON 19 JUN 2003
L15 166 S L14

FILE 'REGISTRY' ENTERED AT 08:12:16 ON 19 JUN 2003
L16 STRUCTURE UPLOADED
L17 46 S L16 FULL SUB=L14

FILE 'CAPLUS' ENTERED AT 08:12:34 ON 19 JUN 2003
L18 160 S L17
L19 STRUCTURE UPLOADED

FILE 'REGISTRY' ENTERED AT 08:13:32 ON 19 JUN 2003

=> s l19 subset=l117
LL17 IS NOT A VALID L#
L-numbers must be in the range L1-L999.
ENTER SUBSET L# OR (END):l17

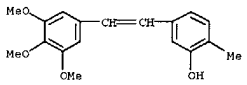
```
ENTER SUBSET SEARCH SCOPE - SAMPLE, FULL, RANGE, OR (END):full
FULL SUBSET SEARCH INITIATED 08:13:56 FILE 'REGISTRY'
FULL SUBSET SCREEN SEARCH COMPLETED -      11 TO ITERATE

100.0% PROCESSED      11 ITERATIONS                              2 ANSWERS
SEARCH TIME: 00.00.01

L20            2 SEA SUB=L17 SSS FUL L19

=> d scan
```

L20 2 ANSWERS REGISTRY COPYRIGHT 2003 ACS
IN Phenol, 2-methyl-5-[2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI)
MF C18 H20 O4

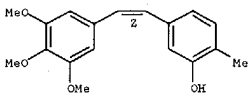


PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

HOW MANY MORE ANSWERS DO YOU WISH TO SCAN? (1):1

L20 2 ANSWERS REGISTRY COPYRIGHT 2003 ACS
IN Phenol, 2-methyl-5-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI)
MF C18 H20 O4

Double bond geometry as shown.



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

ALL ANSWERS HAVE BEEN SCANNED

```
=> fil caplus
COST IN U.S. DOLLARS                                SINCE FILE      TOTAL
                                                       ENTRY    SESSION
FULL ESTIMATED COST                                    35.30     363.50

FILE 'CAPLUS' ENTERED AT 08:14:06 ON 19 JUN 2003
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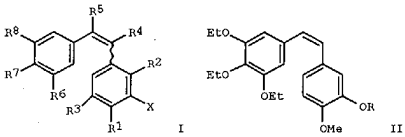
```
FILE COVERS 1907 - 19 Jun 2003  VOL 138 ISS 25
FILE LAST UPDATED: 18 Jun 2003  (20030618/ED)

  This file contains CAS Registry Numbers for easy and accurate
  substance identification.


=> s l20
L21           3 L20

=> d ibib abs hitstr 1-3
```

L21 ANSWER 1 OF 3 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2002:487508 CAPLUS
DOCUMENT NUMBER: 137:47052
TITLE: Preparation of substituted stilbenes as antitumor agents
INVENTOR(S): Hadfield, John Anthony; McGown, Alan Thomson; Mayalarp, Stephen Patrick; Land, Edward John; Hamblett, Ian; Gaukroger, Keira; Lawrence, Nicholas James; Hepworth, Lucy Annette; Butler, John
PATENT ASSIGNEE(S): Cancer Research Ventures Limited, UK
SOURCE: PCT Int. Appl., 76 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002050007	A2	20020627	WO 2001-GB5702	20011220
WO 2002050007	A3	20021017		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
AU 2002016228	A5	20020701	AU 2002-16228	20011220

PRIORITY APPLN. INFO.:
GB 2000-31262 A 20001221
GB 2001-295 A 20010105
WO 2001-GB5702 W 20011220

OTHER SOURCE(S): MARPAT 137:47052
GI



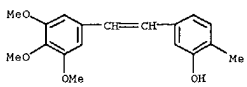
I II

AB Stilbene and quinone compds. related to combretastatin A-4, such as I [X = OH, NO2, amino, aryl, heteroaryl, alkyl, alkoxy, CHO, halogen, haloalkyl, CONH2, O-aryl, O-heteroaryl; R1 = alkyl, CHO, alkoxy, amino, SR, CF3, halogen; R2, R3 = H, alkyl, alkoxy, OH, amino, thio, CF3, halogen; R4, R5 = H, alkyl, CH2NHCOR, CH2CONHR; R6, R7, R8 = H, alkyl, alkoxy; zigzag bond

L21 ANSWER 1 OF 3 CAPLUS COPYRIGHT 2003 ACS (Continued)
= cis-bond or trans-bond], or a salt or deriv. thereof, were prepd. for their use as anticancer compds. and prodrugs. The present invention further relates to the photochem. release of an active form of the compd. from a prodrug conjugate and the photochem. isomerization from a trans to cis form of I. Thus, reaction between 3,4,5-triethoxybenzyltriphenylphosphonium bromide and 3-O-t-butyldimethylsilyl-4-methoxybenzaldehyde yielded cis-stilbene [II; R = TBDMS] which upon desilylation afforded stilbene deriv. II [R = H (III)]. III showed IC50 = 0.018 .mu.M against MTT(K562) cell line.

IT **438534-68-0P**
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of substituted stilbenes as antitumor agents)

RN 438534-68-0 CAPLUS
CN Phenol, 2-methyl-5-[2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)



L21 ANSWER 2 OF 3 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2001:137169 CAPLUS
DOCUMENT NUMBER: 134:178403
TITLE: Preparation and use of cis-stilbenes with vascular damaging activity
INVENTOR(S): Davis, Peter David
PATENT ASSIGNEE(S): Angiogene Pharmaceuticals Ltd., UK
SOURCE: PCT Int. Appl., 17 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001012579	A2	20010222	WO 2000-GB3067	20000809
WO 2001012579	A3	20011011		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
EP 1206429	A2	20020522	EP 2000-951727	20000809
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL				
JP 2003507356	T2	20030225	JP 2001-516880	20000809

PRIORITY APPLN. INFO.:
GB 1999-18912 A 19990812
WO 2000-GB3067 W 20000809

OTHER SOURCE(S): MARPAT 134:178403
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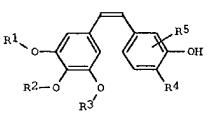

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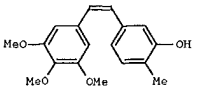


II

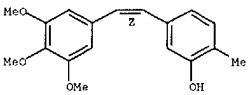
AB Compds. of formula I [wherein; R1, R2 and R3 are alkyl; R4 is (un)substituted alkyl, alkylthio, alkylsulfinyl, alkylsulfonyl, or halo;

L21 ANSWER 2 OF 3 CAPLUS COPYRIGHT 2003 ACS (Continued)
R5 is H, alkoxy, alkyl, alkylthio, hydroxy or halo] are prepd. Five examples are disclosed, one of which is a dihydrogen phosphate ester prodrug. The precursor of example II was prepd. by Wittig olefination of 3,4,5-trimethoxybenzyltriphenylphosphonium bromide and 3-tert-butyldimethylsilyloxy-4-methylbenzaldehyde. Fluoride-mediated deprotection of the silyloxy intermediate provided II as a white solid. Compds. I showed activity against tumor vasculature measured by redn. in functional vascular vol. in a mouse tumor assay (CaNT tumor-bearing mice). These compds. exhibit vascular damaging activity and are therefore potentially of value in treatment of diseases where reversal of neovascularization may have therapeutic benefit.

IT **288585-59-1P**, (Z)-1-(3-Hydroxy-4-methylphenyl)-2-(3,4,5-trimethoxyphenyl)ethene
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(prepn. and use of stilbenes with vascular damaging activity)

RN 288585-59-1 CAPLUS
CN Phenol, 2-methyl-5-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



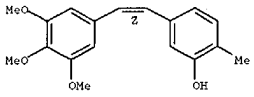
L21 ANSWER 3 OF 3 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2000:592548 CAPLUS
DOCUMENT NUMBER: 133:177486
TITLE: Preparation of substituted stilbene compounds with vascular damaging activity
INVENTOR(S): Davis, Peter David
PATENT ASSIGNEE(S): Angiogene Pharmaceuticals Ltd., UK
SOURCE: PCT Int. Appl., 31 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000048590	A1	20000824	WO 2000-GB503	20000215
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
EP 1154767	A1	20011121	EP 2000-903824	20000215
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
JP 2002537250	T2	20021105	JP 2000-599382	20000215
PRIORITY APPLN. INFO.:			GB 1999-3403 A	19990216
			WO 2000-GB503 W	20000215

OTHER SOURCE(S): MARPAT 133:177486
AB A vascular damaging agent AXB (A = substituted cis-stilbene; X = linker bond, atom, or group; B = moiety derived from an inhibitor of the formation or action of NO in mammalian systems), is claimed. Thus, (Z)-1-[3-(N-.alpha.-tert-butoxycarbonyl-N-.omega.-nitroarginyloxy)-4-methoxyphenyl]-2-(3,4,5-trimethoxyphenyl)ethene was stirred with CF3CO2H in CH2Cl2 to give (Z)-1-(4-methoxy-3-NG-nitroarginyloxyphenyl)-2-(3,4,5-trimethoxyphenyl)ethene. The latter at 50 mg/kg i.p. in mice bearing CaNT or SaS tumors gave 95% redn. in vascular vol. and 91-100% tumor necrosis.
IT **288585-59-1P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(prepn. of substituted stilbene compds. with vascular damaging activity)
RN 288585-59-1 CAPLUS
CN Phenol, 2-methyl-5-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

Double bond geometry as shown.

L21 ANSWER 3 OF 3 CAPLUS COPYRIGHT 2003 ACS (Continued)



REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

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L1              STRUCTURE UPLOADED
L2           41 S L1
L3          675 S L1 FULL

     FILE 'CAPLUS' ENTERED AT 08:08:54 ON 19 JUN 2003
L4          407 S L3

     FILE 'REGISTRY' ENTERED AT 08:09:00 ON 19 JUN 2003
L5              STRUCTURE UPLOADED
L6          108 S L5 FULL SUB=L3

     FILE 'CAPLUS' ENTERED AT 08:09:44 ON 19 JUN 2003
L7          218 S L6

     FILE 'REGISTRY' ENTERED AT 08:09:51 ON 19 JUN 2003
L8              STRUCTURE UPLOADED
L9           76 S L8 FULL SUB=L6

     FILE 'CAPLUS' ENTERED AT 08:10:35 ON 19 JUN 2003
L10         169 S L9
L11             STRUCTURE UPLOADED
                S L11

     FILE 'REGISTRY' ENTERED AT 08:11:31 ON 19 JUN 2003
L12          60 S L11 FULL SUB=L9

     FILE 'CAPLUS' ENTERED AT 08:11:32 ON 19 JUN 2003
L13         166 S L12 SUBSET=L9 FULL

     FILE 'REGISTRY' ENTERED AT 08:11:35 ON 19 JUN 2003
L14          60 S L11 FULL SUB=L9

     FILE 'CAPLUS' ENTERED AT 08:11:44 ON 19 JUN 2003
L15         166 S L14

     FILE 'REGISTRY' ENTERED AT 08:12:16 ON 19 JUN 2003
L16             STRUCTURE UPLOADED
L17          46 S L16 FULL SUB=L14

     FILE 'CAPLUS' ENTERED AT 08:12:34 ON 19 JUN 2003
L18         160 S L17
L19             STRUCTURE UPLOADED

     FILE 'REGISTRY' ENTERED AT 08:13:32 ON 19 JUN 2003
L20           2 S L19  SUB=L17 FULL

     FILE 'CAPLUS' ENTERED AT 08:14:06 ON 19 JUN 2003
L21           3 S L20

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COST IN U.S. DOLLARS                        SINCE FILE      TOTAL
                                              ENTRY     SESSION
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FULL ESTIMATED COST	14.86	378.36

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)	SINCE FILE ENTRY	TOTAL SESSION
CA SUBSCRIBER PRICE	-1.95	-1.95

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Property values tagged with IC are from the ZIC/VINITI data file provided by InfoChem.

STRUCTURE FILE UPDATES: 17 JUN 2003 HIGHEST RN 532924-24-6
DICTIONARY FILE UPDATES: 17 JUN 2003 HIGHEST RN 532924-24-6

TSCA INFORMATION NOW CURRENT THROUGH JANUARY 6, 2003

Please note that search-term pricing does apply when conducting SmartSELECT searches.

Crossover limits have been increased. See HELP CROSSOVER for details.

Experimental and calculated property data are now available. See HELP PROPERTIES for more information. See STNote 27, Searching Properties in the CAS Registry File, for complete details:
http://www.cas.org/ONLINE/STN/STNOTES/stnotes27.pdf

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L22 STRUCTURE UPLOADED

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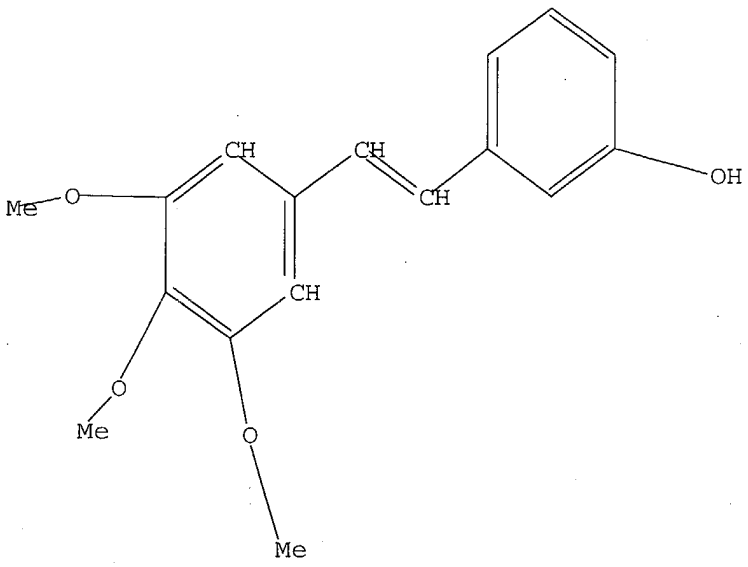

Structure attributes must be viewed using STN Express query preparation.

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L3 675 S L1 FULL

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L4 407 S L3

FILE 'REGISTRY' ENTERED AT 08:09:00 ON 19 JUN 2003
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L6 108 S L5 FULL SUB=L3

FILE 'CAPLUS' ENTERED AT 08:09:44 ON 19 JUN 2003
L7 218 S L6

FILE 'REGISTRY' ENTERED AT 08:09:51 ON 19 JUN 2003
L8 STRUCTURE UPLOADED
L9 76 S L8 FULL SUB=L6

FILE 'CAPLUS' ENTERED AT 08:10:35 ON 19 JUN 2003
L10 169 S L9
L11 STRUCTURE UPLOADED
S L11

FILE 'REGISTRY' ENTERED AT 08:11:31 ON 19 JUN 2003

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L12           60 S L11 FULL SUB=L9

     FILE 'CAPLUS' ENTERED AT 08:11:32 ON 19 JUN 2003
L13          166 S L12 SUBSET=L9 FULL

     FILE 'REGISTRY' ENTERED AT 08:11:35 ON 19 JUN 2003
L14           60 S L11 FULL SUB=L9

     FILE 'CAPLUS' ENTERED AT 08:11:44 ON 19 JUN 2003
L15          166 S L14

     FILE 'REGISTRY' ENTERED AT 08:12:16 ON 19 JUN 2003
L16               STRUCTURE UPLOADED
L17           46 S L16 FULL SUB=L14

     FILE 'CAPLUS' ENTERED AT 08:12:34 ON 19 JUN 2003
L18          160 S L17
L19               STRUCTURE UPLOADED

     FILE 'REGISTRY' ENTERED AT 08:13:32 ON 19 JUN 2003
L20            2 S L19  SUB=L17 FULL

     FILE 'CAPLUS' ENTERED AT 08:14:06 ON 19 JUN 2003
L21            3 S L20

     FILE 'REGISTRY' ENTERED AT 08:15:36 ON 19 JUN 2003
L22               STRUCTURE UPLOADED

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FULL SUBSET SEARCH INITIATED 08:22:01 FILE 'REGISTRY'
FULL SUBSET SCREEN SEARCH COMPLETED -      46 TO ITERATE

100.0% PROCESSED      46 ITERATIONS                          35 ANSWERS
SEARCH TIME: 00.00.01

L23           35 SEA SUB=L17 SSS FUL L22

=> fil caplus
COST IN U.S. DOLLARS                                SINCE FILE      TOTAL
                                                       ENTRY    SESSION
FULL ESTIMATED COST                                    39.30     417.66

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)          SINCE FILE      TOTAL
                                                       ENTRY    SESSION
CA SUBSCRIBER PRICE                                     0.00      -1.95

FILE 'CAPLUS' ENTERED AT 08:22:05 ON 19 JUN 2003
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.
COPYRIGHT (C) 2003 AMERICAN CHEMICAL SOCIETY (ACS)
```

FILE COVERS 1907 - 19 Jun 2003 VOL 138 ISS 25
FILE LAST UPDATED: 18 Jun 2003 (20030618/ED)

This file contains CAS Registry Numbers for easy and accurate substance identification.

=> s l23
L24 157 L23

=>
Uploading 10049248.str

L25 STRUCTURE UPLOADED

=> fil reg
COST IN U.S. DOLLARS

	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	0.83	418.49

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)

	SINCE FILE ENTRY	TOTAL SESSION
CA SUBSCRIBER PRICE	0.00	-1.95

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USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.

Property values tagged with IC are from the ZIC/VINITI data file provided by InfoChem.

STRUCTURE FILE UPDATES: 17 JUN 2003 HIGHEST RN 532924-24-6
DICTIONARY FILE UPDATES: 17 JUN 2003 HIGHEST RN 532924-24-6

TSCA INFORMATION NOW CURRENT THROUGH JANUARY 6, 2003

Please note that search-term pricing does apply when conducting SmartSELECT searches.

Crossover limits have been increased. See HELP CROSSOVER for details.

Experimental and calculated property data are now available. See HELP PROPERTIES for more information. See STNote 27, Searching Properties in the CAS Registry File, for complete details:
http://www.cas.org/ONLINE/STN/STNOTES/stnotes27.pdf

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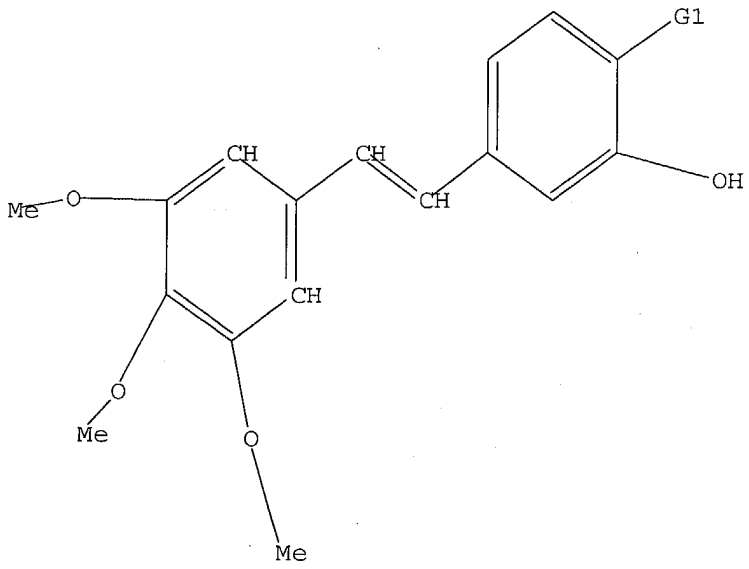
L25 HAS NO ANSWERS
L25 STR



G1 C,S,X

Structure attributes must be viewed using STN Express query preparation.

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L1 STRUCTURE UPLOADED
L2 41 S L1
L3 675 S L1 FULL

FILE 'CAPLUS' ENTERED AT 08:08:54 ON 19 JUN 2003
L4 407 S L3

FILE 'REGISTRY' ENTERED AT 08:09:00 ON 19 JUN 2003
L5 STRUCTURE UPLOADED
L6 108 S L5 FULL SUB=L3

FILE 'CAPLUS' ENTERED AT 08:09:44 ON 19 JUN 2003
L7 218 S L6

FILE 'REGISTRY' ENTERED AT 08:09:51 ON 19 JUN 2003
L8 STRUCTURE UPLOADED
L9 76 S L8 FULL SUB=L6

FILE 'CAPLUS' ENTERED AT 08:10:35 ON 19 JUN 2003
L10 169 S L9
L11 STRUCTURE UPLOADED
S L11

FILE 'REGISTRY' ENTERED AT 08:11:31 ON 19 JUN 2003

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L12           60 S L11 FULL SUB=L9

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L14           60 S L11 FULL SUB=L9

      FILE 'CAPLUS' ENTERED AT 08:11:44 ON 19 JUN 2003
L15          166 S L14

      FILE 'REGISTRY' ENTERED AT 08:12:16 ON 19 JUN 2003
L16               STRUCTURE UPLOADED
L17           46 S L16 FULL SUB=L14

      FILE 'CAPLUS' ENTERED AT 08:12:34 ON 19 JUN 2003
L18          160 S L17
L19               STRUCTURE UPLOADED

      FILE 'REGISTRY' ENTERED AT 08:13:32 ON 19 JUN 2003
L20            2 S L19  SUB=L17 FULL

      FILE 'CAPLUS' ENTERED AT 08:14:06 ON 19 JUN 2003
L21            3 S L20

      FILE 'REGISTRY' ENTERED AT 08:15:36 ON 19 JUN 2003
L22               STRUCTURE UPLOADED
L23           35 S L22  SUB=L17 FULL

      FILE 'CAPLUS' ENTERED AT 08:22:05 ON 19 JUN 2003
L24          157 S L23
L25               STRUCTURE UPLOADED

      FILE 'REGISTRY' ENTERED AT 08:23:33 ON 19 JUN 2003

=> s l25 subset=l23
ENTER SUBSET SEARCH SCOPE - SAMPLE, FULL, RANGE, OR (END):full
FULL SUBSET SEARCH INITIATED 08:23:54 FILE 'REGISTRY'
FULL SUBSET SCREEN SEARCH COMPLETED -       8 TO ITERATE

100.0% PROCESSED       8 ITERATIONS                                 6 ANSWERS
SEARCH TIME: 00.00.01

L26            6 SEA SUB=L23 SSS FUL L25

=> fil caplus
COST IN U.S. DOLLARS                                SINCE FILE      TOTAL
                                                         ENTRY    SESSION
FULL ESTIMATED COST                                      35.30     453.79

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)          SINCE FILE      TOTAL
                                                         ENTRY    SESSION
CA SUBSCRIBER PRICE                                       0.00      -1.95

FILE 'CAPLUS' ENTERED AT 08:23:57 ON 19 JUN 2003
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.
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FILE COVERS 1907 - 19 Jun 2003 VOL 138 ISS 25
FILE LAST UPDATED: 18 Jun 2003 (20030618/ED)

This file contains CAS Registry Numbers for easy and accurate substance identification.

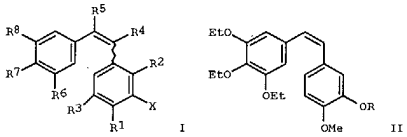
=> s l26
L27 5 L26

=> d ibib abs hitstr 1-5

L27 ANSWER 1 OF 5 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2002:487508 CAPLUS
DOCUMENT NUMBER: 137:47052
TITLE: Preparation of substituted stilbenes as antitumor agents
INVENTOR(S): Hadfield, John Anthony; McGown, Alan Thomson; Mayalarp, Stephen Patrick; Land, Edward John; Hamblett, Ian; Gaukroger, Keira; Lawrence, Nicholas James; Hepworth, Lucy Annette; Butler, John
PATENT ASSIGNEE(S): Cancer Research Ventures Limited, UK
SOURCE: PCT Int. Appl., 76 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002050007	A2	20020627	WO 2001-GB5702	20011220
WO 2002050007	A3	20021017		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
AU 2002016228	A5	20020701	AU 2002-16228	20011220

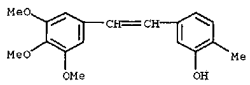
PRIORITY APPLN. INFO.: GB 2000-31262 A 20001221
GB 2001-295 A 20010105
WO 2001-GB5702 W 20011220
OTHER SOURCE(S): MARPAT 137:47052
GI



I II

AB Stilbene and quinone compds. related to combretastatin A-4, such as I [X = OH, NO2, amino, aryl, heteroaryl, alkyl, alkoxy, CHO, halogen, haloalkyl, CONH2, O-aryl, O-heteroaryl; R1 = alkyl, CHO, alkoxy, amino, SR, CF3, halogen; R2, R3 = H, alkyl, alkoxy, OH, amino, thio, CF3, halogen; R4, R5 = H, alkyl, CH2NHCOR, CH2CONHR; R6, R7, R8 = H, alkyl, alkoxy; zigzag bond = cis-bond or trans-bond], or a salt or deriv. thereof, were prepd. for their use as anticancer compds. and prodrugs. The present invention further relates to the photochem. release of an active form of the compd. from a prodrug conjugate and the photochem. isomerization from a trans to cis form of I. Thus, reaction between 3,4,5-triethoxybenzyltriphenylphosphonium bromide and 3-O-t-butyldimethylsilyl-4-methoxybenzaldehyde yielded cis-stilbene [II; R = TBDMS] which upon desilylation afforded stilbene deriv. II [R = H (III)]. III showed IC50 = 0.018 .mu.M against MTT(K562) cell line.

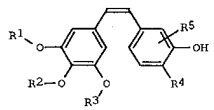
IT **438534-68-0P**
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of substituted stilbenes as antitumor agents)
RN 438534-68-0 CAPLUS
CN Phenol, 2-methyl-5-[2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)



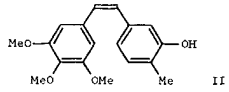
L27 ANSWER 2 OF 5 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2001:137169 CAPLUS
DOCUMENT NUMBER: 134:178403
TITLE: Preparation and use of cis-stilbenes with vascular damaging activity
INVENTOR(S): Davis, Peter David
PATENT ASSIGNEE(S): Angiogene Pharmaceuticals Ltd., UK
SOURCE: PCT Int. Appl., 17 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001012579	A2	20010222	WO 2000-GB3067	20000809
WO 2001012579	A3	20011011		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
EP 1206429	A2	20020522	EP 2000-951727	20000809
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL				
JP 2003507356	T2	20030225	JP 2001-516880	20000809

PRIORITY APPLN. INFO.: GB 1999-18912 A 19990812
WO 2000-GB3067 W 20000809
OTHER SOURCE(S): MARPAT 134:178403
GI



I

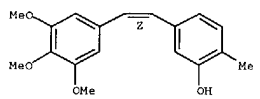


II

AB Compds. of formula I [wherein; R1, R2 and R3 are alkyl; R4 is (un)substituted alkyl, alkylthio, alkylsulfinyl, alkylsulfonyl, or halo; R5 is H, alkoxy, alkyl, alkylthio, hydroxy or halo] are prepd. Five examples are disclosed, one of which is a dihydrogen phosphate ester prodrug. The precursor of example II was prepd. by Wittig olefination of 3,4,5-trimethoxybenzyltriphenylphosphonium bromide and 3-tert-butyldimethylsilyloxy-4-methylbenzaldehyde. Fluoride-mediated deprotection of the silyloxy intermediate provided II as a white solid. Compds. I showed activity against tumor vasculature measured by redn. in functional vascular vol. in a mouse tumor assay (CaNT tumor-bearing mice). These compds. exhibit vascular damaging activity and are therefore potentially of value in treatment of diseases where reversal of neovascularization may have therapeutic benefit.

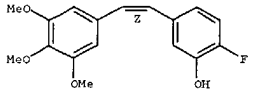
IT **288585-59-1P**, (Z)-1-(3-Hydroxy-4-methylphenyl)-2-(3,4,5-trimethoxyphenyl)ethene
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(prepn. and use of stilbenes with vascular damaging activity)
RN 288585-59-1 CAPLUS
CN Phenol, 2-methyl-5-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



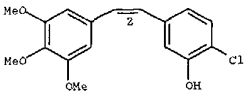
IT **326850-81-1P**, (Z)-1-(4-Fluoro-3-hydroxyphenyl)-2-(3,4,5-trimethoxyphenyl)ethene **326850-82-2P**, (Z)-1-(4-Chloro-3-hydroxyphenyl)-2-(3,4,5-trimethoxyphenyl)ethene **326850-83-3P**, (Z)-1-(4-Ethyl-3-hydroxyphenyl)-2-(3,4,5-trimethoxyphenyl)ethene
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. and use of stilbenes with vascular damaging activity)
RN 326850-81-1 CAPLUS
CN Phenol, 2-fluoro-5-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



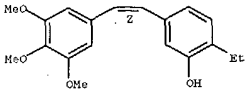
RN 326850-82-2 CAPLUS
CN Phenol, 2-chloro-5-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

L27 ANSWER 2 OF 5 CAPLUS COPYRIGHT 2003 ACS (Continued)
Double bond geometry as shown.

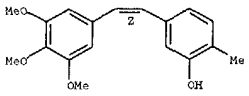


RN 326850-83-3 CAPLUS
CN Phenol, 2-ethyl-5-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



L27 ANSWER 3 OF 5 CAPLUS COPYRIGHT 2003 ACS (Continued)



REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L27 ANSWER 3 OF 5 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2000:592548 CAPLUS
DOCUMENT NUMBER: 133:177486
TITLE: Preparation of substituted stilbene compounds with vascular damaging activity
INVENTOR(S): Davis, Peter David
PATENT ASSIGNEE(S): Angiogene Pharmaceuticals Ltd., UK
SOURCE: PCT Int. Appl., 31 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000048590	A1	20000824	WO 2000-GB503	20000215
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
EP 1154767	A1	20011121	EP 2000-903824	20000215
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
JP 2002537250	T2	20021105	JP 2000-599382	20000215

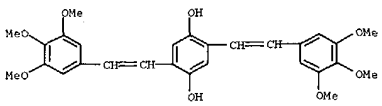
PRIORITY APPLN. INFO.: GB 1999-3403 A 19990216
WO 2000-GB503 W 20000215
OTHER SOURCE(S): MARPAT 133:177486
AB A vascular damaging agent AXB (A = substituted cis-stilbene; X = linker bond, atom, or group; B = moiety derived from an inhibitor of the formation or action of NO in mammalian systems), is claimed. Thus, (Z)-1-{3-(N-.alpha.-tert-butoxycarbonyl-N-.omega.-nitroarginyloxy}-4-methoxyphenyl]-2-(3,4,5-trimethoxyphenyl)ethene was stirred with CF3CO2H in CH2Cl2 to give (Z)-1-(4-methoxy-3-NG-nitroarginyloxyphenyl)-2-(3,4,5-trimethoxyphenyl)ethene. The latter at 50 mg/kg i.p. in mice bearing CaNT or SaS tumors gave 95% redn. in vascular vol. and 91-100% tumor necrosis.
IT 288585-59-1P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(prepn. of substituted stilbene compds. with vascular damaging activity)
RN 288585-59-1 CAPLUS
CN Phenol, 2-methyl-5-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

Double bond geometry as shown.

L27 ANSWER 4 OF 5 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2000:351266 CAPLUS
DOCUMENT NUMBER: 132:345122
TITLE: Sensor comprising an oligomer binding layer and method of making such sensor and arrays of such sensors
INVENTOR(S): Huyberechts, Guido; Jordens, Sven
PATENT ASSIGNEE(S): Interuniversitair Micro-Elektronica Centrum Vzw, Belg.; Universitaire Instituut Antwerpen
SOURCE: Eur. Pat. Appl., 18 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 1003033	A1	20000524	EP 1999-870236	19991116
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
EP 1003032	A1	20000524	EP 1998-870254	19981117
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				

PRIORITY APPLN. INFO.: EP 1998-870254 A 19981117
US 1999-122211P P 19990301
AB An aim of the invention is to provide a new type of sensor, capable of recognizing and/or quantifying analytes in a fluid. A further aim of the present invention is to provide such sensors with an oligomer material as a binding layer. A further aim of the present invention is to provide a novel method for the manuf. of such sensor wherein the oligomer layer is locally deposited on the sites of the sensor having a multitude of sensing sites. A biomol. recognizing an analyte is bound to the oligomer.
IT 270069-97-1P, alkyl derivs.
RL: ARG (Analytical reagent use); DEV (Device component use); RCT (Reactant); SPN (Synthetic preparation); ANST (Analytical study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(as oligomer; sensor comprising oligomer binding layer and method of making such sensor and arrays of such sensors)
RN 270069-97-1 CAPLUS
CN 1,4-Benzenediol, 2,5-bis[2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 7 THERE ARE 7 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L27 ANSWER 5 OF 5 CAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 2000:351265 CAPLUS
DOCUMENT NUMBER: 132:345121
TITLE: Sensor comprising an oligomer binding layer and method of making such sensor and arrays of such sensors
INVENTOR(S): Huyberechts, Guido; Jordens, Sven
PATENT ASSIGNEE(S): Interuniversitair Micro-Elektronica Centrum Vzw, Belg.; Universitaire Instelling Antwerpen
SOURCE: Eur. Pat. Appl., 14 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

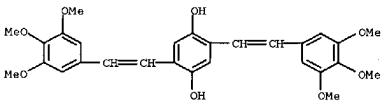
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 1003032	A1	20000524	EP 1998-870254	19981117
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
EP 1003033	A1	20000524	EP 1999-870236	19991116
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
US 2002048751	A1	20020425	US 1999-441118	19991117

PRIORITY APPLN. INFO.: EP 1998-870254 A 19981117
US 1999-122211P P 19990301

AB An aim of the invention is to provide a new type of sensor, capable of recognizing and/or quantifying analytes in a fluid. A further aim of the present invention is to provide such sensors with an oligomer material as a binding layer. A further aim of the present invention is to provide a novel method for the manuf. of such sensor wherein the oligomer layer is locally deposited on the sites of the sensor having a multitude of sensing sites. A biomol. recognizing an analyte is bound to the oligomer.

IT **270069-97-1DP**, alkyl derivs.
RL: ARG (Analytical reagent use); DEV (Device component use); RCT (Reactant); SPN (Synthetic preparation); ANST (Analytical study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(as oligomer; sensor comprising oligomer binding layer and method of making such sensor and arrays of such sensors)

RN 270069-97-1 CAPLUS
CN 1,4-Benzenediol, 2,5-bis[2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 7 THERE ARE 7 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L27 ANSWER 5 OF 5 CAPLUS COPYRIGHT 2003 ACS (Continued)

=> d ibib abs hitstr 124 1-157

L24 ANSWER 1 OF 157 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2003:434278 CAPLUS
TITLE: Combination bacteriolytic therapy for the treatment of tumors
INVENTOR(S): Dang, Long; Kinzler, Kenneth W.; Vogelstein, Bert
PATENT ASSIGNEE(S): The Johns Hopkins University, USA
SOURCE: PCT Int. Appl., 33 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003045153	A1	20030605	WO 2002-US37509	20021121

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 2001-331786P P 20011121

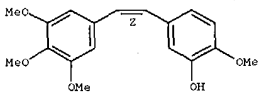
AB Current chemotherapeutic approaches for cancer are in part limited by the inability of drugs to destroy neoplastic cells within poorly vascularized compartments of tumors. We have here systematically assessed anaerobic bacteria for their capacity to grow expansively within avascular compartments of transplanted tumors. Among 26 different strains tested, one (Clostridium novyi) appeared particularly promising. We created a strain of C. novyi devoid of its lethal toxin (C. novyi-NT) and showed that i.v. injected C. novyi-NT spores germinated within the avascular regions of tumors in mice and destroyed surrounding viable tumor cells. When C. novyi-NT spores were administered together with conventional chemotherapeutic drugs, extensive hemorrhagic necrosis of tumors often developed within 24 h, resulting in significant and prolonged anti-tumor effects. This strategy, called combination bacteriolytic therapy (COBALT), has the potential to add a valuable dimension to the treatment of cancer.

IT **117048-59-6**, combretastatin A-4
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(combination bacteriolytic therapy for treatment of tumors)

RN 117048-59-6 CAPLUS
CN Phenol, 2-methoxy-5-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

Double bond geometry as shown.

L24 ANSWER 1 OF 157 CAPLUS COPYRIGHT 2003 ACS (Continued)



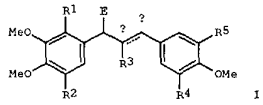
L24 ANSWER 2 OF 157 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2003:376801 CAPLUS
DOCUMENT NUMBER: 138:385212
TITLE: Combretastatin A4 derivatives having antineoplastic activity
INVENTOR(S): Lawrence, Nicholas James; Hadfield, John Anthony; McGown, Alan Thomson; Butler, John; Ducki, Sylvie; Rennison, David; Woo, Meiki
PATENT ASSIGNEE(S): Paterson Institute for Cancer Research, UK; University of Manchester Institute of Science and Technology
SOURCE: PCT Int. Appl., 89 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003040077	A1	20030515	WO 2002-GB5055	20021108

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: GB 2001-26889 A 20011108

GI



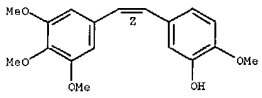
I

AB Compds., such as I [E = oxo, OH; R1, R2 = H, alkoxy; R3 = H, CH2NH2, CH2OH, alkyl, alkylaminomethyl, etc.; R4 = H, halogen; R5 = H, alkoxy, halogen; .alpha.,.beta.-bond = single or double], were prepd. and were designed to mimic the activity of combretastatin A-4 based on chalcone, aurone, or indanone structures, or involving benzoquinone or quinone rings. These compds. are useful for the treatment of cancer or a condition involving abnormal proliferation of vasculature, diabetic retinopathy, psoriasis or endometriosis. Thus, MW 47 I [E = oxo, R1 = R3 = R4 = H, R2 = OMe, R5 = NO2, .alpha.,.beta.-bond = (E)-double] was prepd. with 61% yield by reaction of 3,4,5-trimethoxyacetophenone and 4-methoxy-3-nitrobenzaldehyde using a sodium hydroxide water soln. in MeOH. The anti-cancer activity of exemplified compds. was demonstrated in a range of in vitro and in vivo assays.

IT **117048-59-6DP**, Combretastatin A4, analogs
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of combretastatin A4 analogs having antineoplastic activity)

RN 117048-59-6 CAPLUS
CN Phenol, 2-methoxy-5-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



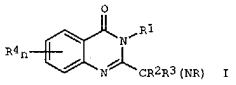
REFERENCE COUNT: 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L24 ANSWER 3 OF 157 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2003:376563 CAPLUS
DOCUMENT NUMBER: 138:385439
TITLE: Preparation of quinazolinone mitotic kinesin inhibitors for treating cancer
INVENTOR(S): Fraley, Mark E.; Hoffman, William F.
PATENT ASSIGNEE(S): Merck & Co., Inc., USA
SOURCE: PCT Int. Appl., 101 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003039460	A2	20030515	WO 2002-US35111	20021101

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 2001-344453P P 20011107
GI

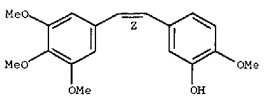


I

AB The present invention relates to quinazolinones (shown as I; variables defined below; e.g. 3-benzyl-2-[1-(4-methylpiperazin-1-yl)propyl]quinazolin-4(3H)-one) that are useful for treating cellular proliferative diseases, for treating disorders assocd. with KSP kinesin activity, and for inhibiting KSP kinesin. The invention also related to compns. which comprise these compds., and methods of using them to treat cancer in mammals. Twelve examples of I were found in a kinesin ATPase in vitro assay to have IC50 .ltoreq.50 .mu.M. Although the methods of prepn. are not claimed, 1 example prepn. of I and characterization data for another 10 examples of I are included. For I: NR = 5-12 membered N-contg. heterocycle, which is optionally substituted with 1-6 R5 groups and which optionally incorporates 1-2 addnl. heteroatoms = N, O and S in the heterocycle; a = 0, 1; b = 0, 1; m = 0-2; n = 0-4; R1 = H, C1-C10 alkyl, aryl, C2-C10 alkenyl, C2-C10 alkynyl, C1-C6 perfluoroalkyl, C3-C8 cycloalkyl, and heterocyclyl. R2 and R3 = H, (C:O)aObC1-C10 alkyl, (C:O)aObaryl, (C:O)aObC2-C10 alkenyl, (C:O)aObC2-C10 alkynyl, CO2H, C1-C6

L24 ANSWER 3 OF 157 CAPLUS COPYRIGHT 2003 ACS (Continued)
perfluoroalkyl, (C:O)aObC3-C8 cycloalkyl, (C:O)aObheterocyclyl, SO2NR7R8, and SO2C1-C10 alkyl; R4 = (C:O)aObC1-C10 alkyl, (C:O)aObaryl, (C:O)aObC2-C10 alkenyl, (C:O)aObC2-C10 alkynyl, CO2H, halo, OH, ObC1-C6 perfluoroalkyl, (C:O)aNR7R8, CN, (C:O)aObC3-C8 cycloalkyl, (C:O)aObheterocyclyl, SO2NR7R8, and SO2C1-C10 alkyl; R5 is (C:O)aObC1-C10 alkyl, (C:O)aObaryl, C2-C10 alkenyl, C2-C10 alkynyl, (C:O)aOb heterocyclyl, CO2H, halo, CN, OH, ObC1-C6 perfluoroalkyl, Oa(C:O)bNR7R8, oxo, CHO, N(O)R7R8, or C(O)aObC3-C8 cycloalkyl; addnl. details are given in the claims.
IT **117048-59-6**, Combretastatin A-4
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(in combination with quinazolinone mitotic kinesin inhibitors for treating cancer)
RN 117048-59-6 CAPLUS
CN Phenol, 2-methoxy-5-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

Double bond geometry as shown.

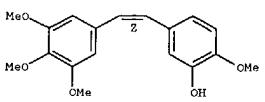


L24 ANSWER 4 OF 157 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2003:376404 CAPLUS
DOCUMENT NUMBER: 138:362737
TITLE: Methods for treating neoplastic, angiogenic, vascular, fibroblastic, and/or immunosuppressive irregularities of the eye and/or joint via administration of combretastatin based medicaments, and iontophoretic devices for delivering combretastatin based medicaments
INVENTOR(S): Parkinson, Thomas M.; Szlek, Malgorzata; Lloyd, Lindsay B.; Vollmer, David L.
PATENT ASSIGNEE(S): USA
SOURCE: U.S. Pat. Appl. Publ., 12 pp.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2003092774	A1	20030515	US 2002-270273	20021011

PRIORITY APPLN. INFO.: US 2001-330212P P 20011017
OTHER SOURCE(S): MARPAT 138:362737
AB A method for treating neoplastic, angiogenic, vascular, fibroblastic, immunosuppressive, infectious, metabolic, and/or constitutional irregularities of the eye and/or joint of a living subject, comprising the steps of: providing a living subject, wherein the living subject includes an affected ocular and/or joint area having a neoplastic, angiogenic, fibroblastic, immunosuppressive, infectious, metabolic, and/or constitutional irregularity; providing a combretastatin-A4 based medicament, wherein the combretastatin-A4 based medicament is capable of preventing microtubule assembly, inhibiting the proliferation of endothelial, eukaryotic, and neoplastic cells, or altering their shape and function, as well as providing an anti-inflammatory effect; assocg. a therapeutically effective concn. of the combretastatin based medicament with the affected ocular and/or joint area of the living subject; and decreasing the neoplastic, angiogenic, vascular, fibroblastic, immunosuppressive, infectious, metabolic and/or constitutional irregularity of the eye and/or joint of the living subject.
IT **117048-59-6**, Combretastatin-A4 **117048-59-6D**, derivs.
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(methods for treating eye and/or joint disorder with combretastatins and iontophoretic devices for delivery)
RN 117048-59-6 CAPLUS
CN Phenol, 2-methoxy-5-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

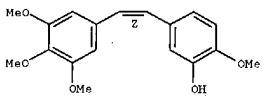
Double bond geometry as shown.



RN 117048-59-6 CAPLUS

L24 ANSWER 4 OF 157 CAPLUS COPYRIGHT 2003 ACS (Continued)
CN Phenol, 2-methoxy-5-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



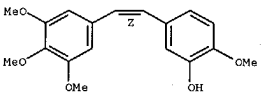
L24 ANSWER 5 OF 157 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2003:356182 CAPLUS
DOCUMENT NUMBER: 138:348759
TITLE: Indolylquinolinone derivative tyrosine kinase inhibitors, preparation thereof, and therapeutic use
INVENTOR(S): Arrington, Kenneth L.; Fraley, Mark E.; Hartman, George D.
PATENT ASSIGNEE(S): Merck & Co., Inc., USA
SOURCE: PCT Int. Appl., 82 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003037252	A2	20030508	WO 2002-US34379	20021025

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 2001-339075P P 20011030
OTHER SOURCE(S): MARPAT 138:348759
AB The invention provides indolylquinolinone compds. which inhibit, regulate, and/or modulate tyrosine kinase signal transduction, compns. which contain these compds., and methods of using them to treat tyrosine kinase-dependent diseases and conditions, such as angiogenesis, cancer, tumor growth, atherosclerosis, age-related macular degeneration, diabetic retinopathy, inflammatory diseases, and the like in mammals. Prepn. of selected compds. is described.
IT **117048-59-6**, Combretastatin A-4
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(indolylquinolinone deriv. tyrosine kinase inhibitors, prepn., therapeutic use, and use with other agents)
RN 117048-59-6 CAPLUS
CN Phenol, 2-methoxy-5-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



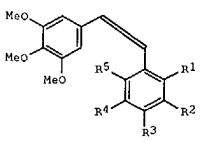
L24 ANSWER 5 OF 157 CAPLUS COPYRIGHT 2003 ACS (Continued)

L24 ANSWER 6 OF 157 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2003:334852 CAPLUS
DOCUMENT NUMBER: 138:353746
TITLE: Preparation of stilbenes as vascular targeting agents (VTAs) for treatment of solid tumors and retinal neovascularization.
INVENTOR(S): Chaplin, David J.; Garner, Charles Manly, III; Kane, Robert Ronald; Pinney, Kevin G.; Prezioso, Joseph Anthony
PATENT ASSIGNEE(S): Oxigene, Inc., USA
SOURCE: PCT Int. Appl., 56 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003035008	A2	20030501	WO 2002-US34497	20021028

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 2001-337348P P 20011026
OTHER SOURCE(S): MARPAT 138:353746
GI

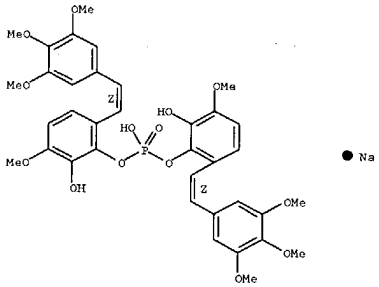


I

AB Title compds. [I; R1, R4, R5 = H, OH, alkoxy, amino, NO2, N3, halo, phosphate ester salt; R2 = H, OH, alkoxy, amino, NO2, amino, phosphate ester (salt); R1R2 = atoms to form a ring; R3 = H, alkoxy, phosphate ester salt], were prepd. Thus, 3,4,5-trimethoxybenzyltriphenylphosphonium bromide (prepn. given) in THF was treated with BuLi in THF at -15.degree.; the mixt. was stirred 30 min. at room temp. followed by addn. of 2-(tert-butyldimethylsilyloxy)-3-bromo-4-methoxybenzaldehyde (prepn. given) and stirring for 3h to give 78.7% E,Z-stilbene deriv., which was stirred with KF and HBr in DMF to give (Z)-2'-hydroxy-3'-bromo-3,4,4',5-tetramethoxystilbene. Tested I at 100 mg/kg i.p. in mice bearing MHEC-5T hemangioendothelioma tumors gave 41-90% blood flow shutdown.
IT **519060-02-7P**

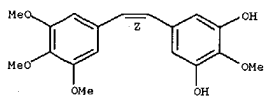
L24 ANSWER 6 OF 157 CAPLUS COPYRIGHT 2003 ACS (Continued)
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(claimed compd.; prepn. of stilbenes as vascular targeting agents (VTAs) for treatment of solid tumors and retinal neovascularization)
RN 519060-02-7 CAPLUS
CN 1,2-Benzenediol, 3-methoxy-6-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]-, 1,1'-(hydrogen phosphate), monosodium salt (9CI) (CA INDEX NAME)

Double bond geometry as shown.



IT **519060-08-3P 519060-09-4P 519060-13-0P 519060-14-1P 519060-17-4P 519060-21-0P 519060-24-3P 519060-27-6P 519060-28-7P 519060-29-8P**
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of stilbenes as vascular targeting agents (VTAs) for treatment of solid tumors and retinal neovascularization)
RN 519060-08-3 CAPLUS
CN 1,3-Benzenediol, 2-methoxy-5-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

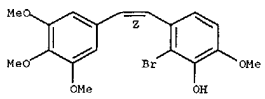
Double bond geometry as shown.



RN 519060-09-4 CAPLUS
CN Phenol, 2-bromo-6-methoxy-3-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]-

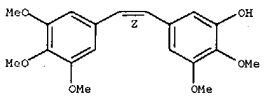
L24 ANSWER 6 OF 157 CAPLUS COPYRIGHT 2003 ACS (Continued)
(9CI) (CA INDEX NAME)

Double bond geometry as shown.



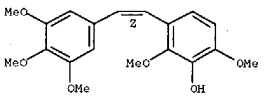
RN 519060-13-0 CAPLUS
CN Phenol, 2,3-dimethoxy-5-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



RN 519060-14-1 CAPLUS
CN Phenol, 2,6-dimethoxy-3-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

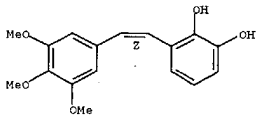
Double bond geometry as shown.



RN 519060-17-4 CAPLUS
CN 1,2-Benzenediol, 3-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

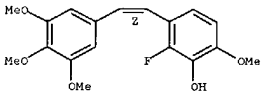
Double bond geometry as shown.

L24 ANSWER 6 OF 157 CAPLUS COPYRIGHT 2003 ACS (Continued)



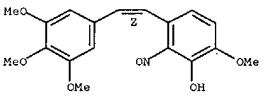
RN 519060-21-0 CAPLUS
CN Phenol, 2-fluoro-6-methoxy-3-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



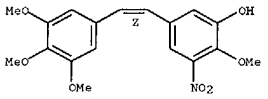
RN 519060-24-3 CAPLUS
CN Phenol, 6-methoxy-2-nitroso-3-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



RN 519060-27-6 CAPLUS
CN Phenol, 2-methoxy-3-nitro-5-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

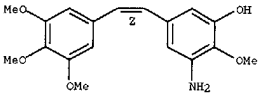
Double bond geometry as shown.



L24 ANSWER 6 OF 157 CAPLUS COPYRIGHT 2003 ACS (Continued)

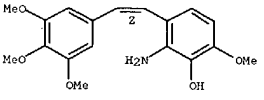
RN 519060-28-7 CAPLUS
CN Phenol, 3-amino-2-methoxy-5-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



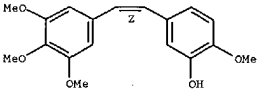
RN 519060-29-8 CAPLUS
CN Phenol, 2-amino-6-methoxy-3-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



IT **117048-59-6**, Combretastatin A4
RL: RCT (Reactant); RACT (Reactant or reagent)
(prepn. of stilbenes as vascular targeting agents (VTAs) for treatment of solid tumors and retinal neovascularization)
RN 117048-59-6 CAPLUS
CN Phenol, 2-methoxy-5-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



L24 ANSWER 7 OF 157 CAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER:	2003:282298 CAPLUS
DOCUMENT NUMBER:	138:297698
TITLE:	Somatostatin or bombesin analog conjugates, and therapeutic and diagnostic uses thereof
INVENTOR(S):	Coy, David H.; Fuselier, Joseph A.; Murphy, William A.; Sun, Lichun
PATENT ASSIGNEE(S):	The Administrators of the Tulane Educational Fund, USA
SOURCE:	PCT Int. Appl., 86 pp. CODEN: PIXXD2
DOCUMENT TYPE:	Patent
LANGUAGE:	English
FAMILY ACC. NUM. COUNT:	1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003028527	A2	20030410	WO 2002-US30143	20020920

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

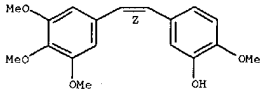
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 2001-323851P P 20010921
OTHER SOURCE(S): MARPAT 138:297698

AB The invention discloses somatostatin and bombesin analog conjugates and uses thereof for targeting compds. useful for detection, diagnosis, and treatment of diseases. The peptide agents of the invention include XYZQ (X = cytotoxic agent, detectable label, etc., or is omitted; Y = peptide increasing hydrophilic biodistribution of agent, hydrophilic polymer including linker for X, omitted; Z = linking peptide; Q = peptide with biol. activity, e.g. somatostatin peptide).

IT **117048-59-6D**, Combretastatin A4, peptide conjugates
RL: DGN (Diagnostic use); PAC (Pharmacological activity); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(somatostatin or bombesin analog conjugates, and therapeutic and diagnostic uses thereof)
RN 117048-59-6 CAPLUS
CN Phenol, 2-methoxy-5-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



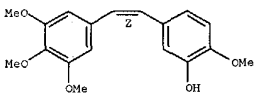
L24 ANSWER 8 OF 157 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2003:261611 CAPLUS
DOCUMENT NUMBER: 138:292740
TITLE: p-Amidobenzyl ethers in drug delivery agents
INVENTOR(S): Senter, Peter D.; Toki, Brian E.
PATENT ASSIGNEE(S): Seattle Genetics, Inc., USA
SOURCE: PCT Int. Appl., 109 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003026577	A2	20030403	WO 2002-US30282	20020924
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
US 2003096743	A1	20030522	US 2001-963103	20010924

PRIORITY APPLN. INFO.: US 2001-963103 A 20010924
US 2002-252947 A 20020923

OTHER SOURCE(S): MARPAT 138:292740
AB Compds. [L-[-An-Z-X-Ww-]-D and B-[-Z-X-Ww-]-D, where D is a drug moiety, L is a ligand, B is a blocking group, A = acyl Z = amino acid or a peptide, X = aminobenzyl ether spacer group, W = optional second group, n = 0 or 1, and w = 0 or 1] and compns. of the compds. with carriers, diluents and/or excipients, and methods of delivery of the drugs are disclosed. Thus, etoposide was allowed to react with a peptide-contg. and the product obtained was shown to be very stable at pH 5.1 and 7.2 after 7 days.
IT **117048-59-6**, Combretastatin A4
RL: RCT (Reactant); THU (Therapeutic use); BIOL (Biological study); RACT (Reactant or reagent); USES (Uses)
(amidobenzyl ethers as drug delivery agents)
RN 117048-59-6 CAPLUS
CN Phenol, 2-methoxy-5-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



L24 ANSWER 8 OF 157 CAPLUS COPYRIGHT 2003 ACS (Continued)

L24 ANSWER 9 OF 157 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2003:259780 CAPLUS
DOCUMENT NUMBER: 138:281082
TITLE: Methods for evaluating treatment efficacy on Kaposi's Sarcoma using angiogenesis associated gene marker
INVENTOR(S): Van Der Kuyl, Antoinette C.; Cornelissen, Marion
PATENT ASSIGNEE(S): Primagen Holding B.V., Neth.
SOURCE: Eur. Pat. Appl., 94 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

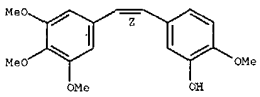
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 1298221	A1	20030402	EP 2001-203703	20010928
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
EP 1225233	A2	20020724	EP 2002-75264	20020123
EP 1225233	A3	20030108		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
WO 2002059558	A2	20020801	WO 2002-NL51	20020123
WO 2002059558	A3	20030109		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				

PRIORITY APPLN. INFO.: EP 2001-200228 A 20010123
EP 2001-203703 A 20010928
US 2001-325722P P 20010928

AB The invention provides a method for detg. whether a treatment is effective in changing the status of a certain set of target cells, such as a tumor, in a patient. This method implies obtaining a sample from a patient after initiation of a treatment, and detg. whether said sample comprises an expression product of at least one marker gene. Preferably, said sample is a blood sample. In one aspect, said expression product is expressed by a peripheral blood mononuclear cell. Said marker gene may be a gene involved in the generation, maintenance and/or breakdown of blood vessels (angiogenesis). A method of the invention is very suitable to det. within a few days if a certain treatment against Kaposi's Sarcoma is successful. Moreover, this method is suitable for detg. the presence of angiogenesis and/or tumor cells in a patient.
IT **117048-59-6**, Combretastatin A-4
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(methods for evaluating treatment efficacy on Kaposi's Sarcoma using angiogenesis assocd. gene marker)
RN 117048-59-6 CAPLUS
CN Phenol, 2-methoxy-5-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

Double bond geometry as shown.

L24 ANSWER 9 OF 157 CAPLUS COPYRIGHT 2003 ACS (Continued)



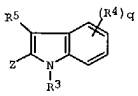
REFERENCE COUNT: 9 THERE ARE 9 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L24 ANSWER 10 OF 157 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2003:242336 CAPLUS
DOCUMENT NUMBER: 138:271678
TITLE: Preparation of substituted 2-(indazolyl)indoles as tyrosine kinase inhibitors
INVENTOR(S): Arrington, Kenneth L.; Fraley, Mark E.; Hanney, Barbara; Kim, Yuntae; Spencer, Keith L.
PATENT ASSIGNEE(S): Merck & Co., Inc., USA
SOURCE: PCT Int. Appl., 117 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003024969	A1	20030327	WO 2002-US28779	20020910

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 2001-322075P P 20010914
OTHER SOURCE(S): MARPAT 138:271678
GI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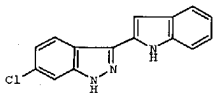
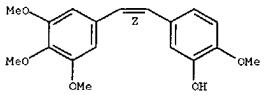

II

AB Title compds. I [Z = indazolyl, etc.; q = 1-3; R3 = H, (CO)O0-1-alkyl, aryl, etc.; R4 = (CO)0-100-1-alk(en/yn)yl, (CO)0-100-1-aryl, COOH, halo, etc.; R5 = H, (CO)0-100-1-alk(en/yn)yl, (CO)0-100-1-aryl, COOH, halo, OH, etc.] are prepd. For instance, 6-chloroindazole (prepn. given) is converted to the corresponding 3-iodo deriv. (EtOH, Ag2SO4, I2), coupled to 1-(tert-butoxycarbonyl)indole-2-boronic acid (prepn. given) (dioxane, Pd(PPh3)4, LiCl, Na2CO3, 80.degree.) and the resulting coupled product deprotected (CH2Cl2, TFA, Me2S) to afford II. I inhibit, regulate and/or modulate tyrosine kinase signal transduction and are useful for the treatment of angiogenesis, cancer, tumor growth, atherosclerosis, age related macular degeneration, diabetic retinopathy, inflammatory diseases.
IT **117048-59-6**, Combretastatin A-4
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)

L24 ANSWER 10 OF 157 CAPLUS COPYRIGHT 2003 ACS (Continued)
(combination pharmaceutical; prepn. of substituted 2-(indazolyl)indoles as tyrosine kinase inhibitors)
RN 117048-59-6 CAPLUS
CN Phenol, 2-methoxy-5-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



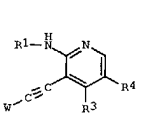
REFERENCE COUNT: 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L24 ANSWER 11 OF 157 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2003:242301 CAPLUS
DOCUMENT NUMBER: 138:271674
TITLE: Preparation of substituted 3-amino-4-(indazolyl)isoquinolines as tyrosine kinase inhibitors
INVENTOR(S): Kim, Yuntae; Escudero, Irma P.
PATENT ASSIGNEE(S): Merck & Co., Inc., USA
SOURCE: PCT Int. Appl., 84 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003024931	A1	20030327	WO 2002-US28735	20020910

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 2001-322043P P 20010914
OTHER SOURCE(S): MARPAT 138:271674
GI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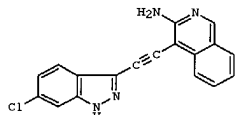
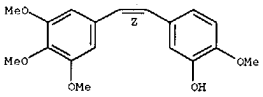

II

AB Title compds. I [R1 = H, alkyl; W = (hetero)aryl; R3-4 = H, (CO)0-100-1-alk(en/yn)yl, (CO)0-100-1-aryl, COOH, halo, etc.] are prepd. For instance, 6-chloroindazole (prepn. given) is converted to the corresponding 3-iodo deriv. (EtOH, Ag2SO4, I2), coupled to 4-ethynylisoquinolin-3-ylamine (prepn. given from 3-aminoisoquinoline) (CH3CN, Pd(PPh3)4, CuI, Et3N, 80.degree., 3 h) to afford II. I inhibit, regulate and/or modulate tyrosine kinase signal transduction and are useful for the treatment of angiogenesis, cancer, tumor growth, atherosclerosis, age related macular degeneration, diabetic retinopathy, inflammatory diseases.
IT **117048-59-6**, Combretastatin A-4
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(combination pharmaceutical; substituted 3-amino-4-(indazolyl)isoquinolines as tyrosine kinase inhibitors)
RN 117048-59-6 CAPLUS
CN Phenol, 2-methoxy-5-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA

L24 ANSWER 11 OF 157 CAPLUS COPYRIGHT 2003 ACS (Continued)
INDEX NAME)

Double bond geometry as shown.



REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

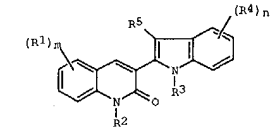
L24 ANSWER 12 OF 157 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2003:202621 CAPLUS
DOCUMENT NUMBER: 138:238027
TITLE: Preparation of 3-(2-indolyl)quinolin-2(1H)-ones as tyrosine kinase inhibitors
INVENTOR(S): Peckham, Jennifer P.; Hoffman, William F.; Arrington, Kenneth L.; Fraley, Mark E.; Hartman, George D.; Kim, Yuntae; Hanney, Barbara; Spencer, Keith L.
PATENT ASSIGNEE(S): Merck & Co., Inc., USA
SOURCE: PCT Int. Appl., 143 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003020699	A2	20030313	WO 2002-US27114	20020826
WO 2003020699	A3	20030522		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 2001-316123P P 20010830
GI

L24 ANSWER 12 OF 157 CAPLUS COPYRIGHT 2003 ACS (Continued)



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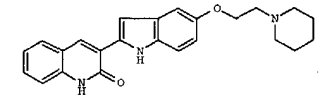
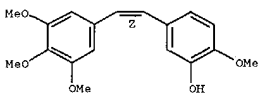


II

AB Title compds., including I (R groups undefined), were prepd. and inhibitors, regulators, and/or modulators of tyrosine kinase signal transduction. For example, 1-(tert-butoxycarbonyl)-5-[(tert-butyldimethylsilyl)oxy]-1H-indol-2-ylboronic acid was coupled with 2-chloro-3-iodoquinoline (prepn. of starting materials given) in the presence of Pd(PPh3)4 and K3PO4 in dioxane to give the protected 3-(2-indolyl)quinoline deriv. Deprotection using triethylamine trihydrofluoride afforded the alc. Reaction with 1-(2-chloroethyl)piperidine.bul.HCl and Cs2CO3 in DMF followed by reflux at 110.degree. in AcOH and H2O for 12 h provided II. Compds. of the invention inhibited VEGF-stimulated mitogenesis of human vascular endothelial cells in culture with IC50 values between 0.01 .mu.M - 5.0 .mu.M. Thus, I and compns. contg. I are useful for the treatment of tyrosine kinase-dependent diseases and conditions, such as angiogenesis, cancer, tumor growth, atherosclerosis, age related macular degeneration, diabetic retinopathy, inflammatory diseases, and the like in mammals (no data).
IT **117048-59-6**, Combretastatin A-4
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(combination therapy; prepn. of (indolyl)quinolinones for treatment of cancer, atherosclerosis, inflammatory diseases, and other tyrosine kinase-dependent conditions)
RN 117048-59-6 CAPLUS
CN Phenol, 2-methoxy-5-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

Double bond geometry as shown.

L24 ANSWER 12 OF 157 CAPLUS COPYRIGHT 2003 ACS (Continued)



L24 ANSWER 13 OF 157 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2003:202525 CAPLUS
DOCUMENT NUMBER: 138:243276
TITLE: Vascular implants containing combretastatin A-4 or combretastatin A-4 phosphate
INVENTOR(S): Wnendt, Stephan; Chaplin, David; Kuttler, Bernd; Lorenz, Guenter
PATENT ASSIGNEE(S): Oxygene Inc., USA
SOURCE: PCT Int. Appl., 61 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003020331	A1	20030313	WO 2002-EP9836	20020903

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

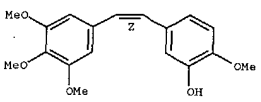
DE 10142897	A1	20030320	DE 2001-10142897	20010903
DE 10142881	A1	20030403	DE 2001-10142881	20010903

PRIORITY APPLN. INFO.: DE 2001-10142881 A 20010903
DE 2001-10142897 A 20010903

AB The invention relates to implants, in particular intracavernous or intravascular implants, preferably for the treatment or prophylaxis of coronary or peripheral vascular occlusion, strictures or stenosis, in particular for the prophylaxis of restenosis. The implants contain combretastatin A-4 or combretastatin A-4 phosphate that is chem. bonded in a covalent or non-covalent form or is in a phys. fixed form. Stents prepd. from alloys, polymers or their combination, also with alumina coating are treated with the alc. soln. of combretastatin A-4 or combretastatin A-4 phosphate under sterile condition. According to an other method combretastatin A-4 or combretastatin A-4 phosphate are included in a biodegradable polymer for coating. Other drugs can be added to the implants.
IT **117048-59-6**, Combretastatin A-4
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(vascular implants contg. combretastatin A-4 or combretastatin A-4 phosphate)
RN 117048-59-6 CAPLUS
CN Phenol, 2-methoxy-5-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

Double bond geometry as shown.

L24 ANSWER 13 OF 157 CAPLUS COPYRIGHT 2003 ACS (Continued)



REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

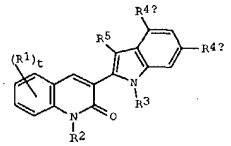
L24 ANSWER 14 OF 157 CAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 2003:202476 CAPLUS
DOCUMENT NUMBER: 138:238026
TITLE: Preparation of indolinylquinolinones as tyrosine kinase inhibitors with therapeutic uses
INVENTOR(S): Kim, Yuntae; Hanney, Barbara; Spencer, Keith L.; Hartman, George D.; Arrington, Kenneth L.
PATENT ASSIGNEE(S): Merck & Co., Inc., USA
SOURCE: PCT Int. Appl., 90 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003020276	A1	20030313	WO 2002-US27161	20020826

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 2001-315897P P 20010830
OTHER SOURCE(S): MARPAT 138:238026
GI



I

AB The present invention relates to indolinylquinolinones (shown as I; variables defined below; e.g. 3~[6-[(4-methylpiperazin-1-yl)carbonyl]-1H-indol-2-yl]quinolin-2(1H)-one) which inhibit, regulate and/or modulate tyrosine kinase signal transduction, compns. which contain these compds., and methods of using them to treat tyrosine kinase-dependent diseases and conditions, such as angiogenesis, cancer, tumor growth, atherosclerosis, age related macular degeneration, diabetic retinopathy, inflammatory

L24 ANSWER 14 OF 157 CAPLUS COPYRIGHT 2003 ACS (Continued)

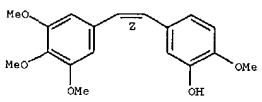
diseases, and the like in mammals. For I; a = 0 or 1; b = 0 or 1; n = 0, 1, or 2; t = 1 or 2; R1 and R5 = H, (C:O)aObC1-C10 alkyl, (C:O)aObaryl, (C:O)aObC2-C10 alkenyl, (C:O)aObC2-C10 alkynyl, CO2H, halo, OH, ObC1-C6 perfluoroalkyl, (C:O)aNR7R8, CN, (C:O)aObC3-C8 cycloalkyl, and (C:O)aObheterocyclyl. R2 and R3 = H, (C:O)aC1-C6 alkyl, (C:O)aaryl, C1-C6 alkyl, SO2Ra, and aryl; R4a or R4b = H and the other = (C:O)aObC1-C10 alkyl, (C:O)aObaryl, (C:O)aObC2-C10 alkenyl, (C:O)aObC2-C10 alkynyl, CO2H, halo, OH, ObC1-C6 perfluoroalkyl, (C:O)aNR7R8, CN, (C:O)aObC3-C8 cycloalkyl, and (C:O)aObheterocyclyl. R7 and R8 = H, (C:O)ObC1-C10 alkyl, (C:O)ObC3-C8 cycloalkyl, (C:O)Obaryl, (C:O)Obheterocyclyl, C1-C10 alkyl, aryl, C2-C10 alkenyl, C2-C10 alkynyl, heterocyclyl, C3-C8 cycloalkyl, SO2Ra, (C:O)N(Rb)2, or R7 and R8 can be taken together with the N to which they are attached to form a monocyclic or bicyclic heterocycle with 5-7 members in each ring and optionally contg., in addn. to the N, one or two addnl. heteroatoms = N, O and S; Ra = (C1-C6)alkyl, (C3-C6)cycloalkyl, aryl, or heterocyclyl; and Rb is H, (C1-C6)alkyl, aryl, heterocyclyl, (C3-C6)cycloalkyl, (C:O)OC1-C6 alkyl, (C:O)C1-C6 alkyl or S(O)2Ra. Compds. I inhibit VEGF-stimulated mitogenesis of human vascular endothelial cells in culture with IC50 values = 0.01-5.0 .mu.M. Although the methods of prepn. are not claimed, 3 example prepns. are included.

IT **117048-59-6**, Combretastatin A-4
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(combined with indolinylquinolinone tyrosine kinase inhibitors for treatments and/or prevention of various disorders)

RN 117048-59-6 CAPLUS

CN Phenol, 2-methoxy-5-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

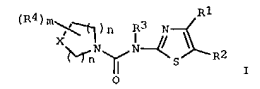
L24 ANSWER 15 OF 157 CAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 2003:154246 CAPLUS
DOCUMENT NUMBER: 138:187764
TITLE: Preparation of 2-(azacyclylcarbonylamino)thiazoles as tyrosine kinase inhibitors
INVENTOR(S): Hartman, George D.; Tucker, Thomas J.; Sisko, John T.; Smith, Anthony M.; Lumma, William C., Jr.
PATENT ASSIGNEE(S): Merck & Co., Inc., USA
SOURCE: PCT Int. Appl., 101 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

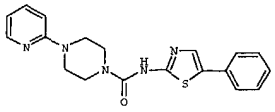
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003015778	A1	20030227	WO 2002-US27156	20020813

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 2001-313234P P 20010817
OTHER SOURCE(S): MARPAT 138:187764
GI



I



II

AB Title ureas I [wherein X = CH or NR3a; m = 1-6; n = independently 0-2; R1 = H, halo, alkyl, or alkoxy; R2 = (un)substituted aryl, CN, CONRaRb, halo, cycloalkyl, or C.tplbond.CRc; R3 = H, alkyl, SO2Rd, CORd, or CO2Rd; R3a = per the definition of R3 or substitutad alkyl; R4 = H, alkylene-NR5R6, CO2H, CO2Rd, halo, OH, alkoxy, or (un)substituted alkyl; R5 and R6 = independently H, alkyl, SO2Rd, CO2Rd, CORd, alkylene-NRaRb,

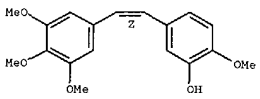
L24 ANSWER 15 OF 157 CAPLUS COPYRIGHT 2003 ACS (Continued)
alkylene-CONRaRb, or (un)substituted alkylene-heterocyclyl or aryl; or NR5R6 = (un)substituted heterocyclyl; Ra and Rb = independently H, (cyclo)alkyl, Ph, CO2Rd, CORd, or SO2Rd; Rc = H, Ph, or alkyl; Rd = Ph or alkyl; or pharmaceutically acceptable salts or stereoisomers thereof] were prepd. for the inhibition, regulation, and/or modulation tyrosine kinase signal transduction. For example, reaction of 2-[(4-nitrophenoxycarbonyl)amino]-5-phenylthiazole with 4-(2-pyridyl)piperazine in the presence of DIEA in DMF at 60.degree. for 1 h gave II. Tested I inhibited VEGF-stimulated mitogenesis of human vascular endothelial cells in culture with IC50 values between 0.01 - 5.0 .mu.M. I are useful for the treatment of tyrosine kinase-dependent diseases and conditions, such as angiogenesis, cancer, tumor growth, atherosclerosis, age related macular degeneration, diabetic retinopathy, inflammatory diseases, and the like in mammals (no data).

IT **117048-59-6**, Combretastatin A-4
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(combination therapy agent; prepn. of (azacyclylcarbonylamino)thiazole tyrosine kinase inhibitors as angiogenesis inhibitors)

RN 117048-59-6 CAPLUS

CN Phenol, 2-methoxy-5-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



REFERENCE COUNT: 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

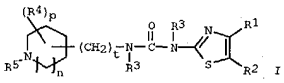
L24 ANSWER 16 OF 157 CAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 2003:154204 CAPLUS
DOCUMENT NUMBER: 138:165738
TITLE: Tyrosine kinase inhibitors and their use in disease treatment
INVENTOR(S): Hartman, George D.; Tucker, Thomas J.; Sisko, John T.; Smith, Anthony M.; Lumma, William C., Jr.
PATENT ASSIGNEE(S): Merck & Co., Inc., USA
SOURCE: PCT Int. Appl., 58 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003015717	A2	20030227	WO 2002-US27149	20020813

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 2001-313374P P 20010817
OTHER SOURCE(S): MARPAT 138:165738
GI



AB The present invention relates to compds. I (n = 1,2,3; p,t = 1,2; R1 = H, halo, C1-8-alkyl; R2 = Ph, CN, C(:O)NRaRb, halo, C3-6-cycloalkyl, C.tplbond.CRc; R4 = H, halo, OH, C1-8-alkyl, C1-8-alkoxy; R5 = H, Ph, C1-8-alkyl, CO2Rd, C(:O)Rd, SO2Rd; Ra,Rb = H, Ph, C1-8-alkyl, CO2Rd, C(:O)Rd, SO2Rd; Rc = H, Ph, C1-8-alkyl; Rd = Ph, C1-8-alkyl, benzyl) which inhibit, regulate and/or modulate tyrosine kinase signal transduction. I may be used to treat tyrosine kinase-dependent diseases and conditions, such as angiogenesis, cancer, tumor growth, atherosclerosis, age related macular degeneration, diabetic retinopathy, inflammatory diseases, and the like in mammals. Thus, compds. such as N-(5-phenylthiazol-2-yl)-N'-(4-aminopiperidin-4-yl)urea were prepd. and tested for effects on VEGF receptor kinase, FLT-1 kinase, and HUVEC mitogenesis. I compds. inhibited HUVEC mitogenesis with IC50 values of 0.01-5.0 .mu.M.

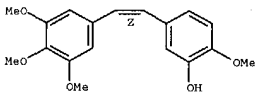
IT **117048-59-6**, Combretastatin A-4

L24 ANSWER 16 OF 157 CAPLUS COPYRIGHT 2003 ACS (Continued)
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(pharmaceuticals contg. tyrosine kinase inhibitors and; tyrosine kinase inhibitors and their use in disease treatment)

RN 117048-59-6 CAPLUS

CN Phenol, 2-methoxy-5-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



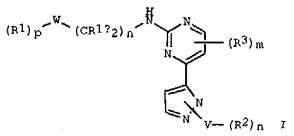
L24 ANSWER 17 OF 157 CAPLUS COPYRIGHT 2003 ACS

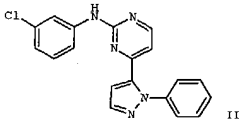
ACCESSION NUMBER: 2003:117807 CAPLUS
DOCUMENT NUMBER: 138:153548
TITLE: Preparation of 4-(pyrazolyl)-2-pyrimidinamines as tyrosine kinase inhibitors
INVENTOR(S): Fraley, Mark E.; Peckham, Jennifer P.; Arrington, Kenneth L.; Hoffman, William F.; Hartman, George D.
PATENT ASSIGNEE(S): Merck & Co., Inc., USA
SOURCE: PCT Int. Appl., 96 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003011837	A1	20030213	WO 2002-US23879	20020726

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 2001-309399P P 20010801
OTHER SOURCE(S): MARPAT 138:153548
GI





AB The present invention relates to title compds. I [wherein R1a = H, (un)substituted alkyl, OR8, or N(R8)2; R1 and R2 = independently H, halo, CF3, (CH2)tR9COR8, COR9, (CH2)tOR8, CN, (CH2)tNR7R8, (CH2)tCONR7R8, CO2R8,

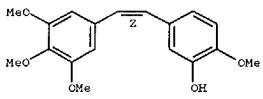
L24 ANSWER 17 OF 157 CAPLUS COPYRIGHT 2003 ACS (Continued)
(CH2)tSO0-2(CH2)tNR7R8, or (un)substituted (cyclo)alkyl, aryl, heterocyclyl, alkenyl, or alkynyl; R3 = independently H, CN, halo, N(R3)2, (CH2)tOR8, or (un)substituted (ar)alkyl or aryl; R7 = independently H or (un)substituted (ar)alkyl; R8 = independently H or (un)substituted (cyclo)alkyl, aryl, heterocyclyl, or aralkyl; or NR7R8 = (un)substituted heterocyclyl; R9 = independently (un)substituted heterocyclyl, alkyl, or aryl; V = a bond, aryl, or heterocyclyl; W = aryl or heterocyclyl; m = 0-2; n = 0-6; p = 0-4; t = independently 0-6; and pharmaceutically acceptable salts, hydrates, and stereoisomers thereof], which inhibit, regulate and/or modulate tyrosine kinase signal transduction, compns. which contain these compds., and methods of using them to treat tyrosine kinase-dependent diseases and conditions. For example, 2-(methylthio)pyrimidine-4-carboxylic acid was amidated with dimethylhydroxylamine.bul.HCl in the presence of EDC and TEA, and the product treated with MeMgBr in Et2O to give 1-[2-(methylthio)pyrimidin-4-yl]ethanone. Coupling with N,N-dimethylformamide dimethylacetal followed by cyclization with phenylhydrazine afforded 2-(methylthio)-4-(1-phenyl-1H-pyrazol-3/5-yl)pyrimidine. Oxidn. with oxone and reaction with 3-chloroaniline provided the 4-(pyrazolyl)-2-pyrimidinamine II. In bioassays, I inhibited VEGF-stimulated mitogenesis of human vascular endothelial cells in culture with IC50 values between 0.01 .mu.M and 5.0 .mu.M. Thus, I are useful for the treatment of angiogenesis, cancer, tumor growth, atherosclerosis, age related macular degeneration, diabetic retinopathy, inflammatory diseases, and the like in mammals (no data).

IT **117048-59-6**, Combretastatin A-4
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(compn. component; prepn. of (pyrazolyl)pyrimidinamine tyrosine kinase inhibitors for treatment of angiogenesis, cancer, atherosclerosis, inflammatory diseases, and other tyrosine kinase-dependent conditions)

RN 117048-59-6 CAPLUS

CN Phenol, 2-methoxy-5-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



REFERENCE COUNT: 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L24 ANSWER 18 OF 157 CAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 2003:117806 CAPLUS
DOCUMENT NUMBER: 138:153547
TITLE: Preparation of 4-(imidazolyl)-2-pyrimidinamines as tyrosine kinase inhibitors
INVENTOR(S): Bilodeau, Mark T.; Manley, Peter J.; Balitza, Adrienne; Rodman, Leonard; Hartman, George D.
PATENT ASSIGNEE(S): Merck & Co., Inc., USA
SOURCE: PCT Int. Appl., 105 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003011836	A1	20030213	WO 2002-US23764	20020726

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
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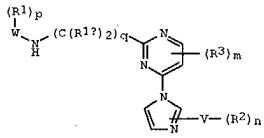
PRIORITY APPLN. INFO.: US 2001-309400P P 20010801
OTHER SOURCE(S): MARPAT 138:153547
GI



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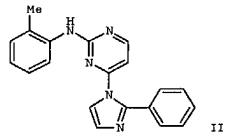


II

L24 ANSWER 18 OF 157 CAPLUS COPYRIGHT 2003 ACS (Continued)

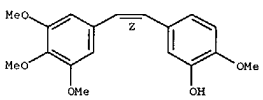
AB The present invention relates to title compds. I [wherein R1a = H, (un)substituted alkyl, or OR8, or N(R8)2; R1 and R2 = independently H, halo, CF3, (CH2)tR9COR8, COR9, (CH2)tOR8, CN, (CH2)tNR7R8, (CH2)tCONR7R8, CO2R8, (CH2)tSOq(CH2)tNR7R8, oxido, or (un)substituted (cyclo)alkyl, aryl, heterocyclyl, alkenyl, or alkynyl; R3 = H, CN, halo, N(R8)2, (CH2)tOR8, or (un)substituted (ar)alkyl or aryl; R7 = independently H or (un)substituted (ar)alkyl; R8 = independently H or (un)substituted (cyclo)alkyl, aryl, heterocyclyl, or aralkyl; or NR7R8 = (un)substituted heterocyclyl; R9 = independently (un)substituted heterocyclyl, alkyl, or aryl; V = bond, aryl, or heterocyclyl; W = aryl or heterocyclyl; m = 0-3; n = 0-6; p = 0-4; q = undefined; t = 0-6; or pharmaceutically acceptable salts, hydrates or stereoisomers thereof], which inhibit, regulate and/or modulate tyrosine kinase signal transduction, compns. which contain these compds., and methods of using them to treat tyrosine kinase-dependent diseases and conditions. For example, 2-phenylimidazole was coupled with 4-chloro-2-(methylthio)pyrimidine in the presence of NaH in DMF and the product oxidized using sodium tungstate dihydrate and H2O2 in EtOAc to give 2-(methylsulfonyl)-4-(2-phenyl-1H-imidazol-1-yl)pyrimidine. Substitution with 2-methylaniline and purifn. by reverse phase chromatog. afforded II.bul.TFA. In bioassays, I inhibited VEGF-stimulated mitogenesis of human vascular endothelial cells in culture with IC50 values between 0.01 .mu.M and 5.0 .mu.M. Thus, I are useful for the treatment of angiogenesis, cancer, tumor growth, atherosclerosis, age related macular degeneration, diabetic retinopathy, inflammatory diseases, and the like in mammals (no data).

IT **117048-59-6**, Combretastatin A-4
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(prepn. of (imidazolyl)pyrimidinamines as tyrosine kinase inhibitors)

RN 117048-59-6 CAPLUS

CN Phenol, 2-methoxy-5-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

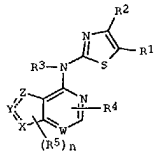
L24 ANSWER 19 OF 157 CAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 2003:97306 CAPLUS
DOCUMENT NUMBER: 138:137303
TITLE: Preparation of fused heterocycle substituted aminothiazolecarbonitriles as tyrosine kinase inhibitors
INVENTOR(S): Bilodeau, Mark T.; Manley, Peter J.; Hartman, George D.
PATENT ASSIGNEE(S): Merck & Co., Inc., USA
SOURCE: PCT Int. Appl., 84 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003009852	A1	20030206	WO 2002-US23191	20020719

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 2001-307443P P 20010724
OTHER SOURCE(S): MARPAT 138:137303
GI



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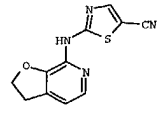


II

AB The present invention relates to the prepn. of title compds. I [wherein X, Y, and Z = C, S, N, or O, provided that at least one of X, Y, or Z = C; W = C or N; n = 0-6; R1, R2, and R4 = independently H, perfluoroalkyl(oxy), OH, CN, halo, or (un)substituted (CO)rOs-alkyl, (CO)rOs-alkenyl, (CO)rOs-alkynyl, (CO)rOs-aryl, (CO)rOs-heterocyclyl, or alkyl-NRaRb; R3 = H, SO2Rc, (CO)rRc, or CO2Rc; R5 = R3 or Or(CO)sNRaRb, halo, OH, oxo, perfluoroalkyl(oxy), CHO, CO2H, CN, or (un)substituted (CO)rOs-aryl, (CO)rOs-heterocyclyl, or (CO)rOs-alkyl; r = 0-1; s = 0-1; Ra and Rb = independently H, SO2Rc, CO2Rc, or (un)substituted (CO)r-alkyl, (CO)r-heterocyclyl, or (CO)r-aryl; or NRaRb = (un)substituted monocyclic or bicyclic heterocycle; Rc = (un)substituted alkyl, aryl, benzyl, or

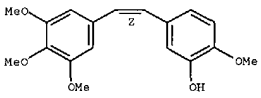
L24 ANSWER 19 OF 157 CAPLUS COPYRIGHT 2003 ACS (Continued)
heterocyclyl; or pharmaceutically acceptable salts or stereoisomers thereof], which inhibit, regulate, and/or modulate tyrosine kinase signal transduction, compns. which contain these compds., and methods of using them to treat tyrosine kinase-dependent diseases and conditions. For example, 7-bromofuro[2,3-c]pyridine was converted to the amine using benzophenone imine, NaOBu-t, racemic BINAP, and Pd2(dba)3 in dry toluene and then hydrogenated with 10% Pd/C in AcOH to give 2,3-dihydrofuro[2,3-c]pyridin-7-amine. Addn. of 2-chloro-5-cyanothiazole in the presence of NaH in THF afforded the (furopyridinylamino)thiazolecarbonitrile II. In bioassays, I inhibited VEGF-stimulated mitogenesis of human vascular endothelial cells in culture with IC50 values between 0.001 .mu.M and 5.0 .mu.M. Thus, I are useful for the treatment of angiogenesis, cancer, tumor growth, atherosclerosis, age related macular degeneration, diabetic retinopathy, inflammatory diseases, and the like in mammals (no data).

IT **117048-59-6**, Combretastatin A-4
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(compn. component; prepn. of fused heterocycle substituted aminothiazolecarbonitriles as tyrosine kinase inhibitors)

RN 117048-59-6 CAPLUS

CN Phenol, 2-methoxy-5-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L24 ANSWER 20 OF 157 CAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 2003:57889 CAPLUS

DOCUMENT NUMBER: 138:112414

TITLE: Compositions and methods of administering tubulin-binding agents for the treatment of ocular diseases

INVENTOR(S): Sherris, David; Wood, Mark

PATENT ASSIGNEE(S): Oxigene, Inc., USA

SOURCE: PCT Int. Appl., 59 pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003006002	A1	20030123	WO 2002-US22449	20020715

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 2002-377556P P 20020502
US 2002-377845P P 20020503

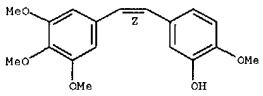
AB The present invention is directed to the administration of vascular targeting agents, particularly a tubulin-binding agent, for the treatment of ocular neovascularization, ocular tumors, and conditions such as diabetic retinopathy, retinopathy of prematurity, retinoblastoma and macular degeneration.

IT **117048-59-6**, Combretastatin A4
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(compns. and methods of administering tubulin-binding agents for the treatment of ocular diseases)

RN 117048-59-6 CAPLUS

CN Phenol, 2-methoxy-5-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



REFERENCE COUNT: 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS

L24 ANSWER 20 OF 157 CAPLUS COPYRIGHT 2003 ACS (Continued)
RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L24 ANSWER 21 OF 157 CAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 2003:20798 CAPLUS

DOCUMENT NUMBER: 138:221804

TITLE: Antineoplastic Agents. 487. Synthesis and Biological Evaluation of the Antineoplastic Agent 3,4-Methylenedioxy-5,4'-dimethoxy-3'-amino-Z-stilbene and Derived Amino Acid Amides

AUTHOR(S): Pettit, George R.; Anderson, Collin R.; Herald, Delbert L.; Jung, M. Katherine; Lee, Debbie J.; Hamel, Ernest; Pettit, Robin K.

CORPORATE SOURCE: Cancer Research Institute and Department of Chemistry and Biochemistry, Arizona State University, Tempe, AZ, 85287-2404, USA

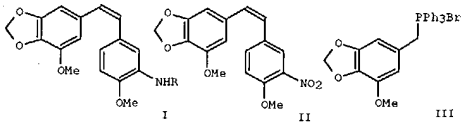
SOURCE: Journal of Medicinal Chemistry (2003), 46(4), 525-531
CODEN: JMCMAR; ISSN: 0022-2623

PUBLISHER: American Chemical Society

DOCUMENT TYPE: Journal

LANGUAGE: English

GI



AB An efficient synthesis of 3,4-methylenedioxy-5,4'-dimethoxy-3'-amino-Z-stilbene, I (R = H), and its hydrochloride salt is reported. Nitrostilbene II was obtained via a Wittig reaction using phosphonium bromide III and 3-nitro-4-methoxybenzaldehyde. A one-step redn. of II using zinc in acetic acid produced I (R = H). The coupling of I (R = H) with various Fmoc amino acids (Cys, Gly, Phe, Ser, Trp, Tyr, Val), followed by cleavage of the .alpha.-amine protecting group, resulted in a series of new cancer cell growth inhibitory amides. I (R = H), its HCl salt, glycine amide I (R = COCH2NH2), and tyrosine amide I [R = COCH(CH2C6H4OH-4)NH2] had the highest level (GI50 = 10-2-10-3 .mu.g/mL) of activity against a panel of six human and one animal (P388) cancer cell lines. I (R = H) and its hydrochloride salt potently inhibited tubulin polymn. by binding at the colchicine site, while the amino acid amides had little activity against purified tubulin. Nevertheless, most of the amides caused a marked increase in the mitotic index of treated cells, indicating that tubulin was their intracellular target.

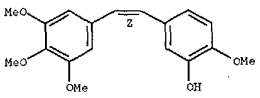
IT **117048-59-6**, Combretastatin A4
RL: PAC (Pharmacological activity); BIOL (Biological study)
(prepn. and biol. evaluation of amino acid amides of Z-stilbene derivs. as antineoplastic and antimicrobial agents)

RN 117048-59-6 CAPLUS

CN Phenol, 2-methoxy-5-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

Double bond geometry as shown.

L24 ANSWER 21 OF 157 CAPLUS COPYRIGHT 2003 ACS (Continued)



REFERENCE COUNT: 29 THERE ARE 29 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L24 ANSWER 22 OF 157 CAPLUS COPYRIGHT 2003 ACS (Continued)

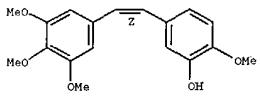
ylmethyl]piperazine-1-carboxylic acid methylamide show enhanced pharmacokinetic properties as compared to previously reported thiazolylaminopyridines in WO 01/17995 A1. Although the methods of prepn. are not claimed, 13 example prepns. are included.

IT **117048-59-6**, Combretastatin A-4
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(in combination with thiazolylaminopyridine tyrosine kinase inhibitors for various therapies)

RN 117048-59-6 CAPLUS

CN Phenol, 2-methoxy-5-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



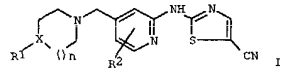
REFERENCE COUNT: 7 THERE ARE 7 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L24 ANSWER 22 OF 157 CAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 2003:5956 CAPLUS
DOCUMENT NUMBER: 138:73254
TITLE: Preparation of thiazolylaminopyridines as tyrosine kinase inhibitors with therapeutic uses
INVENTOR(S): Bilodeau, Mark T.; Hartman, George D.
PATENT ASSIGNEE(S): Merck & Co., Inc., USA
SOURCE: PCT Int. Appl., 93 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003000687	A1	20030103	WO 2002-US21110	20020618
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
US 2003100567	A1	20030529	US 2002-174774	20020619

PRIORITY APPLN. INFO.: US 2001-300245P P 20010622
OTHER SOURCE(S): MARPAT 138:73254
GI



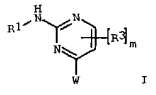
AB The present invention relates to thiazolylaminopyridines (shown as I; variables defined below; e.g. 4-[2-(5-cyanothiazol-2-ylamino)pyridin-4-ylmethyl]piperazine-1-carboxylic acid methylamide) which inhibit, regulate and/or modulate tyrosine kinase signal transduction, compns. which contain these compds., and methods of using them to treat tyrosine kinase-dependent diseases and conditions, such as angiogenesis, cancer, tumor growth, atherosclerosis, age related macular degeneration, diabetic retinopathy, inflammatory diseases, and the like in mammals. For I: n is 0 or 1; X is C-H or N, provided X is C-H if n = 1 and R1 is SO2-(C1-C6 alkyl) and provided that X is C-H if R1 is NH(C:O)NR3H; R1 is SO2(C1-C6 alkyl), (C:O)NR3H, or NH(C:O)NR3H; R2 is H, OH, OC1-C6 alkyl, C1-C6 alkyl, or halo; and R3 is C1-C6 alkyl. Compds. I inhibit VEGF-stimulated mitogenesis of human vascular endothelial cells in culture with IC50 values = 0.01-5.0 .mu.M. 4-[2-(5-Cyanothiazol-2-ylamino)pyridin-4-ylmethyl]piperazine-1-carboxylic acid methylamide, 2-[[4-[[4-(methylsulfonyl)piperidin-1-yl]methyl]pyridin-2-yl]amino]-1,3-thiazole-5-carbonitrile, and 4-[2-(5-cyanothiazol-2-ylamino)-3-methylpyridin-4-

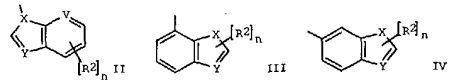
L24 ANSWER 23 OF 157 CAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 2002:977797 CAPLUS
DOCUMENT NUMBER: 138:55974
TITLE: Preparation of 2-anilino-4-(indol-1-yl)pyrimidines as tyrosine kinase inhibitors
INVENTOR(S): Kim, Yuntae; Hanney, Barbara
PATENT ASSIGNEE(S): Merck & Co., Inc., USA
SOURCE: PCT Int. Appl., 82 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002102783	A1	20021227	WO 2002-US18907	20020614
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				

PRIORITY APPLN. INFO.: US 2001-299343P P 20010619
OTHER SOURCE(S): MARPAT 138:55974
GI

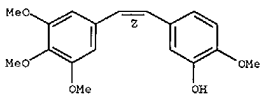




AB The title compds. [I; W = II-IV; X, Y = C, N, provided that when X = N, then Y = C and when X = C, then Y = N; V = C, N; R1 = (un)substituted aryl, heterocyclyl; R2 = H, halo, alkyl, etc.; R3 = H, alkyl, aryl, etc.; m = 0-2; n = 0-5] which inhibit, regulate and/or modulate tyrosine kinase signal transduction, and therefore are useful in treating tyrosine kinase-dependent diseases and conditions, such as angiogenesis, cancer, tumor growth, atherosclerosis, age related macular degeneration, diabetic retinopathy, inflammatory diseases, and the like in mammals, were prepd. E.g., a multi-step synthesis of I [W = 4-fluoro-1H-indol-1-yl; R1 = Ph; R3 = H], starting from 2-thiouracil, was given.

L24 ANSWER 23 OF 157 CAPLUS COPYRIGHT 2003 ACS (Continued)
IT **117048-59-6**, Combretastatin A-4
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(prepn. of 2-anilino-4-(indol-1-yl)pyrimidines as tyrosine kinase inhibitors and their use in combination with)
RN 117048-59-6 CAPLUS
CN Phenol, 2-methoxy-5-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



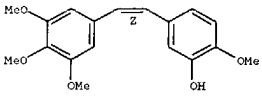
REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L24 ANSWER 24 OF 157 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2002:942701 CAPLUS
DOCUMENT NUMBER: 138:8413
TITLE: Vascular implants treated with FK506
INVENTOR(S): Wnendt, Stephan; Von Oepen, Randolf; Kuttler, Bernd; Lang, Gerhard
PATENT ASSIGNEE(S): Jomed G.m.b.H., Germany
SOURCE: Ger. Offen., 22 pp.
CODEN: GWXXBX
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
DE 10127330	A1	20021212	DE 2001-10127330	20010606

PRIORITY APPLN. INFO.: DE 2001-10127330 20010606
AB The invention concerns vascular implants that include a metal, or an alloy base, a ceramic or polymer coating and covalently bound or phys. immobilized FK506 for the treatment of stenosis and restenosis. In addn., the implants can include other drugs. For the prepn., the coated implant is incubated with a soln. of FK506; or FK506 is added during polymn. coating.
IT **117048-59-6**, Combretastatin A4
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(vascular implants treated with FK506)
RN 117048-59-6 CAPLUS
CN Phenol, 2-methoxy-5-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

Double bond geometry as shown.

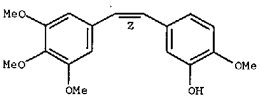


L24 ANSWER 25 OF 157 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2002:941572 CAPLUS
DOCUMENT NUMBER: 138:8411
TITLE: Vascular implants treated with FK506
INVENTOR(S): Wnendt, Stephan; Von Oepen, Randolf; Kuttler, Bernd; Lang, Gerhard
PATENT ASSIGNEE(S): Jomed G.m.b.H., Germany
SOURCE: Ger. Offen., 22 pp.
CODEN: GWXXBX
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
DE 10127011	A1	20021212	DE 2001-10127011	20010605

PRIORITY APPLN. INFO.: DE 2001-10127011 20010605
AB The invention concerns vascular implants that include a metal, or an alloy base, a ceramic or polymer coating and covalently bound or phys. immobilized FK506 for the treatment of stenosis and restenosis. In addn., the implants can include other drugs. For the prepn., the coated implant is incubated with a soln. of FK506; or FK506 is added during polymn. coating.
IT **117048-59-6**, Combretastatin A4
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(vascular implants treated with FK506)
RN 117048-59-6 CAPLUS
CN Phenol, 2-methoxy-5-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

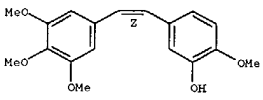
Double bond geometry as shown.



REFERENCE COUNT: 7 THERE ARE 7 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L24 ANSWER 26 OF 157 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2002:925011 CAPLUS
TITLE: Structure-activity and crystallographic analysis of benzophenone derivatives-the potential anticancer agents
AUTHOR(S): Hsieh, Hsing-Pang; Liou, Jing-Ping; Lin, Ying-Ting; Mahindroo, Neeraj; Chang, Jang-Yang; Yang, Yung-Ning; Chern, Shuenn-Shing; Tan, Uan-Kang; Chang, Chun-Wei; Chen, Tung-Wei; Lin, Chi-Hung; Chang, Ying-Ying; Wang, Chiung-Chiu
CORPORATE SOURCE: Sec. 6, Division of Biotechnology and Pharmaceutical Research, National Health Research Institutes, Taipei, Taiwan, 114, Peop. Rep. China
SOURCE: Bioorganic & Medicinal Chemistry Letters (2003), 13(1), 101-105
CODEN: BMCLE8; ISSN: 0960-894X
PUBLISHER: Elsevier Science Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Compds. 1-5, structurally related to combretastatin A-4 showed excellent cytotoxic activities against a panel of human cancer cell lines including multi-drug resistant cell lines. The x-ray three-dimensional structural anal. shows that proton donor in B ring may be required for cytotoxic activity, with intermol. hydrogen bonding playing an important role.
IT INDEXING IN PROGRESS
IT **117048-59-6**, Combretastatin A-4
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(structure-activity and crystallog. anal. of benzophenone derivs. as potential antitumor agents)
RN 117048-59-6 CAPLUS
CN Phenol, 2-methoxy-5-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



REFERENCE COUNT: 27 THERE ARE 27 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

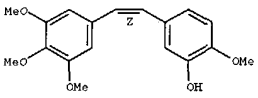
L24 ANSWER 27 OF 157 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2002:793477 CAPLUS
DOCUMENT NUMBER: 137:293582
TITLE: Anti-CD19 immunotoxins and their use in immunotherapy
INVENTOR(S): Olson, William C.; Maddon, Paul J.; Ma, Dangshe
PATENT ASSIGNEE(S): Progenics Pharmaceuticals, Inc., USA
SOURCE: PCT Int. Appl., 46 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002080987	A1	20021017	WO 2002-US9889	20020329

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 2001-282587P P 20010409
AB The invention relates to therapeutic methods using compns. including immunotoxins based on antibodies that specifically bind the B cell membrane protein CD19. Anti-CD19 immunotoxins, compns. contg. such immunotoxins, and methods for using the immunotoxins are provided. The immunotoxins can be labeled with radionuclides, chemotherapeutic agents, or immunomodulators. The immunotoxins can be used in the treatment of B-cell malignancies, various autoimmune diseases, and organ/tissue transplants.
IT **117048-59-6D**, Combretastatin A4, immunotoxin labeled
RL: BSU (Biological study, unclassified); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(anti-CD19 immunotoxins for treatment of B-cell malignancy, autoimmune disease, and transplants)
RN 117048-59-6 CAPLUS
CN Phenol, 2-methoxy-5-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L24 ANSWER 27 OF 157 CAPLUS COPYRIGHT 2003 ACS (Continued)

L24 ANSWER 28 OF 157 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2002:736049 CAPLUS
DOCUMENT NUMBER: 137:253007
TITLE: A combination comprising combretastatin and anticancer agents
INVENTOR(S): Bissery, Marie-Christine
PATENT ASSIGNEE(S): Aventis Pharma S.A., Fr.
SOURCE: PCT Int. Appl., 19 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

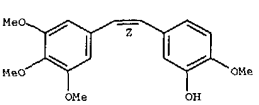
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002074229	A2	20020926	WO 2002-EP3322	20020315

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

US 2002183266	A1	20021205	US 2002-92508	20020308
US 2003060429	A1	20030327	US 2002-97926	20020315

PRIORITY APPLN. INFO.: US 2001-275627P P 20010315
AB An antitumor combination comprising a stilbene deriv. and an anticancer compd. selected from the group consisting of taxanes, alkylating agents, antimetabolites, vinca alkaloids, epidophylloptoxins, and antibiotics as the active ingredients is provided. Methods of using these pharmaceutical prepns. for the treatment of solid carcinomas are also provided. Thus, an infusion formulation contained combretastatin Z hydrochloride 5 mg, Tween-80 0.5 mL and saline soln. 9.5 mL. The combination of , combretastatin Z and cisplatin synergistic.
IT **117048-59-6**, Combretastatin A4
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(combination comprising combretastatin and anticancer agents)
RN 117048-59-6 CAPLUS
CN Phenol, 2-methoxy-5-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

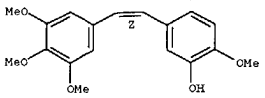
Double bond geometry as shown.



L24 ANSWER 29 OF 157 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2002:682260 CAPLUS
DOCUMENT NUMBER: 138:226477
TITLE: Combretastatin-A4 prodrug induces mitotic catastrophe in chronic lymphocytic leukemia cell line independent of caspase activation and poly(ADP-ribose) polymerase cleavage
AUTHOR(S): Nabha, Sanaa M.; Mohammad, Ramzi M.; Dandashi, Mahmoud H.; Coupaye-Gerard, Brigitte; Aboukameel, Amro; Pettit, George R.; Al-Katib, Ayad M.
CORPORATE SOURCE: Division of Hematology and Oncology, Department of Internal Medicine, Karmanos Cancer Institute, Wayne State University School of Medicine, Detroit, MI, 48201, USA
SOURCE: Clinical Cancer Research (2002), 8(8), 2735-2741
CODEN: CCREF4; ISSN: 1078-0432
PUBLISHER: American Association for Cancer Research
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The authors have previously reported that combretastatin-A4 prodrug (CA4P), an antitubulin/antiangiogenic agent isolated from the South African willow tree Combretum caffrum, induced cell death primarily through mitotic catastrophe in a panel of human B-lymphoid tumors. In this study, the authors investigated the mol. aspects of the mitotic catastrophe and whether or not it shares the same pathways of apoptosis. For this the authors studied the effect of CA4P on selected markers of apoptosis [caspases 9 and 3, poly(ADP-ribose) polymerase (PARP), bcl-2, and bax] and G2-M protein regulators (p53, MDM2, 14-3-3.vsigma., GADD45, cdc2, cdc25, chk1, wee1, p21, and cyclin B1). The chronic lymphocytic leukemia cell line WSU-CLL was used for this purpose. Western blot anal. showed that 24 h of CA4P (5 nM) exposure induces caspase 9 activation and PARP cleavage. However, the addn. of Z-Val²Ala-Asp-fluoromethylketone (a general caspase inhibitor) or Z-Leu-Glu(OMe)-His-Asp(OMe)-CH2F (a caspase 9 inhibitor) before CA4P treatment did not block cell death. No change in bcl-2 or bax protein expression was obsd. Exposure of WSU-CLL cells to 4 and 5 nM CA4P was assocd. with overprodn. of total p53 and no dramatic change in MDM2, 14-3-3.vsigma., GADD45, the cyclin-dependent kinase cdc2, its inhibitory phosphorylation, the cdc2-inhibitory kinase (wee1), chk1, or cdc25 hyperphosphorylation. The overaccumulation of p21 and cyclin B1 protein was obvious at 24 h. Furthermore, CA4P treatment showed an increase in the expression of a marker of mitosis (mitotic protein monoclonal-2 antibody) and an overaccumulation of the cyclin B in the nucleus. The authors' findings suggest that CA4P induces mitotic catastrophe and arrest of WSU-CLL cells mostly in the M phase independent of p53 and independent of chk1 and cdc2 phosphorylation pathways. Apoptosis is a 2ndary mechanism of death in a small proportion of cells through activation of caspase 9 and PARP cleavage. The 2 mechanisms of cell death, i.e., mitotic catastrophe and apoptosis, are independent of each other in the authors' model.
IT **117048-59-6P**, Combretastatin-A4
RL: DMA (Drug mechanism of action); PAC (Pharmacological activity); PUR (Purification or recovery); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(combretastatin-A4 action mechanism in chronic lymphocytic leukemia cells)
RN 117048-59-6 CAPLUS
CN Phenol, 2-methoxy-5-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

Double bond geometry as shown.

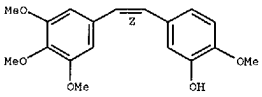
L24 ANSWER 29 OF 157 CAPLUS COPYRIGHT 2003 ACS (Continued)



REFERENCE COUNT: 23 THERE ARE 23 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L24 ANSWER 30 OF 157 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2002:621729 CAPLUS
DOCUMENT NUMBER: 138:147033
TITLE: The biology of the combretastatins as tumour vascular targeting agents
AUTHOR(S): Tozer, Gillian M.; Kanthou, Chryso; Parkins, Charles S.; Hill, Sally A.
CORPORATE SOURCE: Gray Cancer Institute, Middlesex, UK
SOURCE: International Journal of Experimental Pathology (2002), 83(1), 21-38
CODEN: IJEPEI; ISSN: 0959-9673
PUBLISHER: Blackwell Science Ltd.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review. The tumor vasculature is an attractive target for therapy. Combretastatin A-4 (CA-4) and A-1 (CA-1) are tubulin binding agents, structurally related to colchicine, which induce vascular-mediated tumor necrosis in animal models. CA-1 and CA-4 were isolated from the African bush willow, Combretum caffrum, and several synthetic analogs are also now available, such as the Aventis Pharma compd., AVE8062. More sol., phosphated, forms of CA-4 (CA-4-P) and CA-1 (CA-1-P) are commonly used for in vitro and in vivo studies. These are cleaved to the natural forms by endogenous phosphatases and are taken up into cells. The lead compd., CA-4-P, is currently in clin. trial as a tumor vascular targeting agent. In animal models, CA-4-P causes a prolonged and extensive shutdown of blood flow in established tumor blood vessels, with much less effect in normal tissues. This paper reviews the current understanding of the mechanism of action of the combretastatins and their therapeutic potential.
IT **117048-59-6**, Combretastatin A-4
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(biol. of combretastatins as tumor vascular targeting agents)
RN 117048-59-6 CAPLUS
CN Phenol, 2-methoxy-5-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



REFERENCE COUNT: 120 THERE ARE 120 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

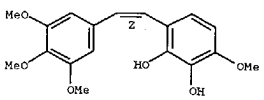
L24 ANSWER 31 OF 157 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2002:555278 CAPLUS
DOCUMENT NUMBER: 137:119643
TITLE: Methods using a combretastatin compound combined with an antitumor agent for modulating tumor growth and metastasis
INVENTOR(S): Lee, Francis Y.; Peck, Ronald; Chaplin, David; Pero, Ronald; Edvardsen, Klaus
PATENT ASSIGNEE(S): Bristol-Myers Squibb Company, USA; Oxigene, Inc.
SOURCE: PCT Int. Appl., 69 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002056692	A1	20020725	WO 2001-US50261	20011220

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 2000-258195P P 20001222
AB Methods and pharmaceutical compns. for modulating tumor growth or metastasis are provided. The methods of the invention use combinations of a combretastatin compd. and an antitumor agent.
IT **109971-63-3**, Combretastatin A1 **109971-63-3D**, Combretastatin A1, derivs. **117048-59-6**, Combretastatin A4 **117048-59-6D**, Combretastatin A4, derivs.
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(combretastatin compd. combined with antitumor agent for modulating tumor growth and metastasis)
RN 109971-63-3 CAPLUS
CN 1,2-Benzenediol, 3-methoxy-6-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

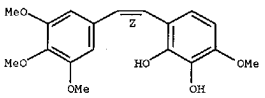
Double bond geometry as shown.



RN 109971-63-3 CAPLUS
CN 1,2-Benzenediol, 3-methoxy-6-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

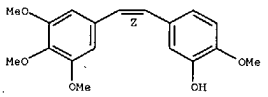
Double bond geometry as shown.

L24 ANSWER 31 OF 157 CAPLUS COPYRIGHT 2003 ACS (Continued)



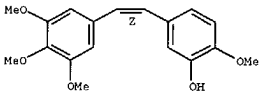
RN 117048-59-6 CAPLUS
CN Phenol, 2-methoxy-5-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



RN 117048-59-6 CAPLUS
CN Phenol, 2-methoxy-5-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

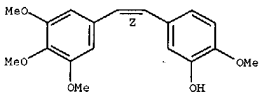
L24 ANSWER 32 OF 157 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2002:521462 CAPLUS
DOCUMENT NUMBER: 137:88442
TITLE: Incensole and furanogermacrens and compounds in treatment for inhibiting neoplastic lesions and microorganisms
INVENTOR(S): Shanahan-Pendergast, Elisabeth
PATENT ASSIGNEE(S): Ire.
SOURCE: PCT Int. Appl., 68 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002053138	A2	20020711	WO 2002-IE1	20020102
WO 2002053138	A3	20020919		

W: AE, AG, AT, AU, BB, BG, CA, CH, CN, CO, CU, CZ, LU, LV, MA, MD, UA, UG, US, VN, YU, RU, TJ, TM
RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, AT, BE, CH, CY, DE, ES, FI, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: IE 2001-2 A 20010102
OTHER SOURCE(S): MARPAT 137:88442
AB The invention discloses the use of incensole and/or furanogermacrens, derivs. metabolites and precursors thereof in the treatment of neoplasia, particularly resistant neoplasia and immundysregulatory disorders. These compds. can be administered alone or in combination with conventional chemotherapeutic, antiviral, antiparasite agents, radiation and/or surgery. Incensole and furanogermacren and their mixt. showed antitumor activity against various human carcinomas and melanomas and antimicrobial activity against Staphylococcus aureus and Enterococcus faecalis.
IT **117048-59-6**, Combretastatin A4
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(pharmaceutical formulation further including; incensole and furanogermacrens and compds. as antitumor and antimicrobial agents)
RN 117048-59-6 CAPLUS
CN Phenol, 2-methoxy-5-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



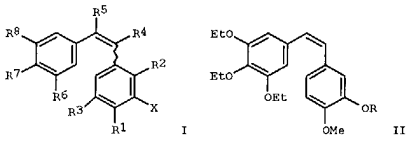
L24 ANSWER 33 OF 157 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2002:487508 CAPLUS
DOCUMENT NUMBER: 137:47052
TITLE: Preparation of substituted stilbenes as antitumor agents
INVENTOR(S): Hadfield, John Anthony; McGown, Alan Thomson; Mayalarp, Stephen Patrick; Land, Edward John; Hamblett, Ian; Gaukroger, Keira; Lawrence, Nicholas James; Hepworth, Lucy Annette; Butler, John
PATENT ASSIGNEE(S): Cancer Research Ventures Limited, UK
SOURCE: PCT Int. Appl., 76 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002050007	A2	20020627	WO 2001-GB5702	20011220
WO 2002050007	A3	20021017		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

AU 2002016228	A5	20020701	AU 2002-16228	20011220
PRIORITY APPLN. INFO.:			GB 2000-31262	A 20001221
			GB 2001-295	A 20010105
			WO 2001-GB5702	W 20011220

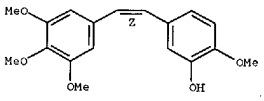
OTHER SOURCE(S): MARPAT 137:47052
GI



AB Stilbene and quinone compds. related to combretastatin A-4, such as I [X = OH, NO2, amino, aryl, heteroaryl, alkyl, alkoxy, CHO, halogen, haloalkyl, CONH2, O-aryl, O-heteroaryl; R1 = alkyl, CHO, alkoxy, amino, SR, CF3,

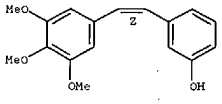
L24 ANSWER 33 OF 157 CAPLUS COPYRIGHT 2003 ACS (Continued)
halogen; R2, R3 = H, alkyl, alkoxy, OH, amino, thio, CF3, halogen; R4, R5 = H, alkyl, CH2NHCOR, CH2CONHR; R6, R7, R8 = H, alkyl, alkoxy; zigzag bond = cis-bond or trans-bond], or a salt or deriv. thereof, were prepd. for their use as anticancer compds. and prodrugs. The present invention further relates to the photochem. release of an active form of the compd. from a prodrug conjugate and the photochem. isomerization from a trans to cis form of I. Thus, reaction between 3,4,5-triethoxybenzyltriphenylphosphonium bromide and 3-O-t-butyldimethylsilyl-4-methoxybenzaldehyde yielded cis-stilbene [II; R = TBDMS] which upon desilylation afforded stilbene deriv. II [R = H (III)]. III showed IC50 = 0.018 .mu.M against MTT(K562) cell line.
IT **117048-59-6**, Combretastatin A-4
RL: PAC (Pharmacological activity); RCT (Reactant); THU (Therapeutic use); BIOL (Biological study); RACT (Reactant or reagent); USES (Uses)
(prepn. of substituted stilbenes as antitumor agents)
RN 117048-59-6 CAPLUS
CN Phenol, 2-methoxy-5-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



IT **160422-43-5P 438534-24-8P 438534-68-0P**
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of substituted stilbenes as antitumor agents)
RN 160422-43-5 CAPLUS
CN Phenol, 3-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

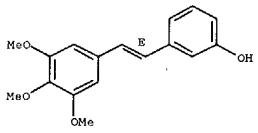
Double bond geometry as shown.



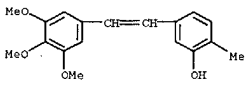
RN 438534-24-8 CAPLUS
CN Phenol, 3-[(1E)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

Double bond geometry as shown.

L24 ANSWER 33 OF 157 CAPLUS COPYRIGHT 2003 ACS (Continued)

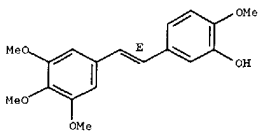


RN 438534-68-0 CAPLUS
CN Phenol, 2-methyl-5-[2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)



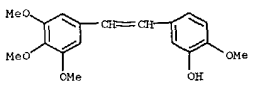
IT **117048-62-1**
RL: RCT (Reactant); RACT (Reactant or reagent)
(prepn. of substituted stilbenes as antitumor agents)
RN 117048-62-1 CAPLUS
CN Phenol, 2-methoxy-5-[(1E)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



IT **438534-81-7P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(prepn. of substituted stilbenes as antitumor agents)
RN 438534-81-7 CAPLUS
CN Phenol, 2-methoxy-5-[2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

L24 ANSWER 33 OF 157 CAPLUS COPYRIGHT 2003 ACS (Continued)



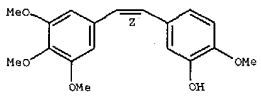
L24 ANSWER 34 OF 157 CAPLUS COPYRIGHT 2003 ACS (Continued)
E-ethenyl halide and a substituted boronic acid in the presence of a palladium catalyst to produce specifically either the Z or E-isomer of substituted stilbenes. Thus, 3-hydroxy-4-methoxybenzaldehyde and 3,4,5-trimethoxyphenylacetic acid were reacted in acetic anhydride with triethylamine, then the product was decarboxylated with copper in quinoline to give II.

IT **117048-59-6P**, Combretastatin A4
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(synthesis of combretastatin A4)

RN 117048-59-6 CAPLUS

CN Phenol, 2-methoxy-5-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

Double bond geometry as shown.

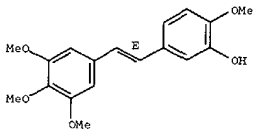


IT **117048-62-1P**, trans-Combretastatin A4
RL: SPN (Synthetic preparation); PREP (Preparation)
(synthesis of combretastatin A4)

RN 117048-62-1 CAPLUS

CN Phenol, 2-methoxy-5-[(1E)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

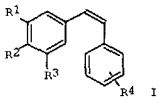
Double bond geometry as shown.



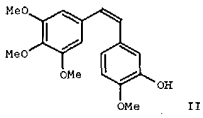
L24 ANSWER 34 OF 157 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2002:487498 CAPLUS
DOCUMENT NUMBER: 137:47051
TITLE: Materials and methods for synthesizing stilbenes
INVENTOR(S): Hadfield, John Anthony; McGown, Alan Thomson; Gaukroger, Keira; Hepworth, Lucy Annette; Lawrence, Nicholas James
PATENT ASSIGNEE(S): Cancer Research Ventures Limited, UK
SOURCE: PCT Int. Appl., 38 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002049994	A2	20020627	WO 2001-GB5534	20011214
WO 2002049994	A3	20021017		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
AU 2002017267	A5	20020701	AU 2002-17267	20011214
PRIORITY APPLN. INFO.:			GB 2000-31263 A	20001221
			WO 2001-GB5534 W	20011214

OTHER SOURCE(S): CASREACT 137:47051; MARPAT 137:47051
GI



I



II

AB The present invention relates materials and methods for synthesizing stilbenes of formula I [R1-R3 = H, OH, NO2, NH2, aryl, heteroaryl, alkyl, alkoxy, halo, etc.; R4 = H, OH, NO2, NH2, alkyl, alkoxy, etc. (one, two or three substituents)], and in particular to processes for the synthesis of substituted stilbenes such as combretastatin A4 (II). The present invention relates in particular to methods which are stereoselective for either the cis or the trans isomer of the substituted stilbene, using a Perkin-type condensation of an arylacetic acid and a substituted benzaldehyde, followed by a decarboxylation reaction to produce the substituted cis-stilbenes or a Suzuki-type reaction involving a Z or

L24 ANSWER 35 OF 157 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2002:471932 CAPLUS
DOCUMENT NUMBER: 137:163285
TITLE: A phase I pharmacokinetic and translational study of the novel vascular targeting agent combretastatin A-4 phosphate on a single-dose intravenous schedule in patients with advanced cancer
AUTHOR(S): Dowlati, Afshin; Robertson, Kelly; Cooney, Matthew; Petros, William P.; Stratford, Michael; Jesberger, John; Rafie, Niusha; Overmoyer, Beth; Makkar, Vinit; Stambler, Bruce; Taylor, Anne; Waas, John; Lewin, Jonathan S.; McCrae, Keith R.; Remick, Scot C.
CORPORATE SOURCE: Division of Hematology/Oncology, Department of Medicine, School of Medicine, Case Western Reserve University (CWRU), Cleveland, OH, 44106, USA
SOURCE: Cancer Research (2002), 62(12), 3408-3416
CODEN: CNREA8; ISSN: 0008-5472
PUBLISHER: American Association for Cancer Research
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Combretastatin A-4 phosphate (CA4P) is a novel antitumor vascular targeting agent, the first agent of this class of compds. to enter the clinic. We performed a Phase I trial to det. the max.-tolerated dose, safety, and pharmacokinetic profile of CA4P on a single-dose i.v. schedule. We also obtained preliminary data on its effect on tumor blood flow using dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) techniques and cell adhesion mols. at the higher-dose levels. Twenty-five assessable patients with advanced cancer received a total of 107 cycles over the following dose escalation schema: 18, 36, 60, 90 mg/m2 as a 10-min infusion and 60 mg/m2 as a 60-min infusion at 3-wk intervals. There was no significant myelotoxicity, stomatitis, or alopecia. Tumor pain was a unique side effect, which occurred in 10% of cycles, and there were four episodes of dose-limiting toxicity at dosages .gtoreq.60 mg/m2, including two episodes of acute coronary syndrome. Pharmacokinetics revealed rapid dephosphorylation of the parent compd. (CA4P) to combretastatin A4 (CA4), with a short plasma half-life (.apprx.30 min). A significant ($P < 0.03$) decline in gradient peak tumor blood flow by DCE-MRI in six of seven patients treated at 60 mg/m2 was obsd. A patient with anaplastic thyroid cancer had a complete response and is alive 30 mo after treatment. The toxicity profile is consistent with a drug that is "vascularly active" and devoid of traditional "cytotoxic" side effects. Dosages .gtoreq.60 mg/m2 as a 10-min infusion define the upper boundary of the max.-tolerated dose.

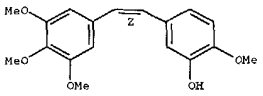
IT **117048-59-6**, Combretastatin A4
RL: ADV (Adverse effect, including toxicity); PAC (Pharmacological activity); PKT (Pharmacokinetics); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(pharmacokinetic and translational study of novel vascular targeting agent combretastatin A-4 phosphate on a single-dose i.v. schedule in patients with advanced cancer)

RN 117048-59-6 CAPLUS

CN Phenol, 2-methoxy-5-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

Double bond geometry as shown.

L24 ANSWER 35 OF 157 CAPLUS COPYRIGHT 2003 ACS (Continued)



REFERENCE COUNT: 14 THERE ARE 14 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

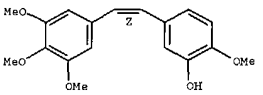
L24 ANSWER 36 OF 157 CAPLUS COPYRIGHT 2003 ACS (Continued)
vascular endothelial growth factor-stimulated mitogenesis of human vascular endothelial cells with IC50 = 0.01-5.0 nM.

IT **117048-59-6**, Combretastatin A-4
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(coadministration; prepn. of pyrimidinylaminothiazoles as tyrosine kinase inhibitors)

RN 117048-59-6 CAPLUS

CN Phenol, 2-methoxy-5-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



L24 ANSWER 36 OF 157 CAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 2002:449449 CAPLUS

DOCUMENT NUMBER: 137:33318

TITLE: Preparation of pyrimidinylaminothiazoles as tyrosine kinase inhibitors.

INVENTOR(S): Bilodeau, Mark T.; Hartman, George D.; Hoffman, Jacob M., Jr.; Lumma, William C., Jr.; Manley, Peter J.; Rodman, Leonard; Sisko, John T.; Smith, Anthony M.; Tucker, Thomas J.

PATENT ASSIGNEE(S): Merck & Co., Inc., USA

SOURCE: PCT Int. Appl., 169 pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

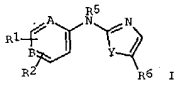
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002045652	A2	20020613	WO 2001-US44573	20011130
WO 2002045652	A3	20020822		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM			
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
US 2002137755	A1	20020926	US 2001-990473	20011121
AU 2002032441	A5	20020618	AU 2002-32441	20011130

PRIORITY APPLN. INFO.: US 2000-251006P P 20001204
WO 2001-US44573 W 20011130

OTHER SOURCE(S): MARPAT 137:33318

GI



AB Title compds. [I; A, B = N, NO; Y = O, S, NR4; R1, R2 = H, perfluoroalkoxy, OH, cyano, halo, (substituted) alkyl(oxy)(carbonyl), aryl(oxy)(carbonyl), heterocyclyl, etc.; R4 = H, aryl, alkyl; R5 = H, SO2Rc, CORc, Rc, CO2Rc; R6 = aryl, cyano, halo, (substituted) alkyl, alkenyl, alkynyl, heterocyclyl, aminocarbonyl; Rc = alkyl, aryl, heterocyclyl], were prepd. for treating angiogenesis, cancer, tumor growth, atherosclerosis, age related macular degeneration, diabetic retinopathy, inflammation, etc. Thus, 4-aminopyrimidine was stirred with NaH in THF; 2-bromo-5-phenylthiazole was added and the mixt. was refluxed overnight to give 5-phenylthiazol-2-yl pyrimidin-4-yl amine. I inhibited

L24 ANSWER 37 OF 157 CAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 2002:348358 CAPLUS

DOCUMENT NUMBER: 137:87838

TITLE: Antineoplastic Agents. 465. Structural Modification of Resveratrol: Sodium Resveratstin Phosphate

AUTHOR(S): Pettit, George R.; Grealish, Matthew P.; Jung, M. Katherine; Hamel, Ernest; Pettit, Robin K.; Chapuis, J. Charles; Schmidt, Jean M.

CORPORATE SOURCE: Cancer Research Institute and Department of Chemistry and Biochemistry, Arizona State University, Tempe, AZ, 85287-2404, USA

SOURCE: Journal of Medicinal Chemistry (2002), 45(12), 2534-2542
CODEN: JMCMAR; ISSN: 0022-2623

PUBLISHER: American Chemical Society

DOCUMENT TYPE: Journal

LANGUAGE: English

OTHER SOURCE(S): CASREACT 137:87838

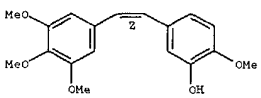
AB As an extension of structure/activity investigations of resveratrol, phenstatin, and the cancer antiangiogenesis drug sodium combretastatin A-4 phosphate, syntheses of certain related stilbenes and benzophenones were undertaken. The tri-Me ether deriv. of (Z)-resveratrol exhibited the strongest activity (GI50 = 0.01-0.001 .mu.g/mL) against a minipanel of human cancer cell lines. A monodemethylated deriv. was converted to prodrug (sodium resveratstin phosphate) for further biol. evaluation. The antitubulin and antimicrobial activities of selected compds. were also evaluated.

IT **117048-59-6**, Combretastatin A-4
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(prepn. and antitumor structure activity relationships of resveratrol analogs)

RN 117048-59-6 CAPLUS

CN Phenol, 2-methoxy-5-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

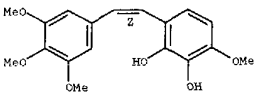
Double bond geometry as shown.



REFERENCE COUNT: 48 THERE ARE 48 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L24 ANSWER 38 OF 157 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2002:255740 CAPLUS
DOCUMENT NUMBER: 137:140374
TITLE: Direct biooxidation of arenes to corresponding catechols with E. coli JM109 (pDTG602). Application to synthesis of combretastatins A-1 and B-1
AUTHOR(S): Bui, Vu P.; Hudlicky, Tomas; Hansen, Trond V.; Stenstrom, Yngve
CORPORATE SOURCE: Department of Chemistry, University of Florida, Gainesville, FL, 32611-7200, USA
SOURCE: Tetrahedron Letters (2002), 43(15), 2839-2841
CODEN: TELEAY; ISSN: 0040-4039
PUBLISHER: Elsevier Science Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 137:140374
AB Convergent syntheses of combretastatins A-1 and B-1 were accomplished via coupling of biocatalytically generated p-bromomethoxycatechol with trimethoxyphenylacetylene.
IT **109971-63-3P**, Combretastatin A-1
RL: SPN (Synthetic preparation); PREP (Preparation)
(prepn. of combretastatins A-1 and B-1 via biooxidn. with E. coli JM109 and coupling of bromomethoxycatechol with (trimethoxyphenyl)acetylene)
RN 109971-63-3 CAPLUS
CN 1,2-Benzenediol, 3-methoxy-6-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

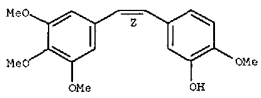
Double bond geometry as shown.



REFERENCE COUNT: 19 THERE ARE 19 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L24 ANSWER 39 OF 157 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2002:243561 CAPLUS
DOCUMENT NUMBER: 137:242112
TITLE: Inhibition of proliferative retinopathy by the anti-vascular agent combretastatin-A4
AUTHOR(S): Griggs, Jeremy; Skepper, Jeremy N.; Smith, Garry A.; Brindle, Kevin M.; Metcalfe, James C.; Hesketh, Robin
CORPORATE SOURCE: Department of Biochemistry, University of Cambridge, Cambridge, CB2 1QW, UK
SOURCE: American Journal of Pathology (2002), 160(3), 1097-1103
CODEN: AJPAA4; ISSN: 0002-9440
PUBLISHER: American Society for Investigative Pathology
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Retinal neovascularization occurs in a variety of diseases including diabetic retinopathy, the most common cause of blindness in the developed world. There is accordingly considerable incentive to develop drugs that target the aberrant angiogenesis assocd. with these conditions. Previous studies have shown that a no. of anti-angiogenic agents can inhibit retinal neovascularization in a well-characterized murine model of ischemia-induced proliferative retinopathy. Combretastatin-A4 (CA-4) is an anti-vascular tubulin-binding agent currently undergoing clin. evaluation for the treatment of solid tumors. We have recently shown that CA-4 is not tumor-specific but elicits anti-vascular effects in nonneoplastic angiogenic vessels. In this study we have examd. the capacity of CA-4 to inhibit retinal neovascularization in vivo. CA-4 caused a dose-dependent inhibition of neovascularization with no apparent side effects. The absence of vascular abnormalities or remnants of disrupted neovessels in retinas of CA-4-treated mice suggests an anti-angiogenic mechanism in this model, in contrast to the anti-vascular effects obsd. against established tumor vessels. Importantly, histol. and immunohistochem. analyses indicated that CA-4 permitted the development of normal retinal vasculature while inhibiting aberrant neovascularization. These data are consistent with CA-4 eliciting tissue-dependent anti-angiogenic effects and suggest that CA-4 has potential in the treatment of nonneoplastic diseases with an angiogenic component.
IT **117048-59-6**, Combretastatin-A4
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(inhibition of proliferative retinopathy by combretastatin-A4)
RN 117048-59-6 CAPLUS
CN Phenol, 2-methoxy-5-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



REFERENCE COUNT: 43 THERE ARE 43 CITED REFERENCES AVAILABLE FOR THIS

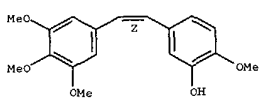
L24 ANSWER 39 OF 157 CAPLUS COPYRIGHT 2003 ACS (Continued)
RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L24 ANSWER 40 OF 157 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2002:220602 CAPLUS
DOCUMENT NUMBER: 136:268115
TITLE: Combretastatin A-4 phosphate prodrug mono- and di-organic amine salts, mono- and di- amino acid salts, and mono- and di-amino acid ester salts
INVENTOR(S): Venit, John J.; Dali, Mandar V.; Dali, Manisha M.; Huang, Yande; Dahlheim, Charles E.; Tejwani, Ravindra W.
PATENT ASSIGNEE(S): Bristol-Myers Squibb Company, USA
SOURCE: PCT Int. Appl., 84 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002022626	A1	20020321	WO 2001-US28401	20010912
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
US 2002072507	A1	20020613	US 2001-950500	20010911
AU 2001090771	A5	20020326	AU 2001-90771	20010912
BR 2001007210	A	20030225	BR 2001-7210	20010912
NO 2002002270	A	20020701	NO 2002-2270	20020513
PRIORITY APPLN. INFO.:			US 2000-232568P P	20000914
			US 2000-251921P P	20001207
			WO 2001-US28401 W	20010912

OTHER SOURCE(S): MARPAT 136:268115
AB Provided herein are novel and useful combretastatin A-4 prodrug salts that increase the soly. of combretastatin A-4, readily regenerate combretastatin A-4 in vivo under normal physiol. conditions, and which produce physiol. tolerable products as a result of the regeneration of combretastatin A-4.
IT **117048-59-6**, Combretastatin A-4
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(combretastatin A-4 phosphate prodrug mono- and di-org. amine salts, mono- and di- amino acid salts, and mono- and di-amino acid ester salts)
RN 117048-59-6 CAPLUS
CN Phenol, 2-methoxy-5-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



L24 ANSWER 40 OF 157 CAPLUS COPYRIGHT 2003 ACS (Continued)

REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

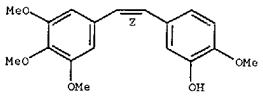
L24 ANSWER 41 OF 157 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2002:180157 CAPLUS
DOCUMENT NUMBER: 138:55697
TITLE: Synthesis of disodium combretastatin A-4 3'-O-phosphate
AUTHOR(S): Zhao, Huiping; Chen, Guorong; Li, Yuanchao
CORPORATE SOURCE: Department of Fine Chemistry, East China University of Science + Technology, Shanghai, 200237, Peop. Rep. China
SOURCE: Zhongguo Yiyao Gongye Zazhi (2001), 32(12), 531-532, 535
CODEN: ZYGZEA; ISSN: 1001-8255
PUBLISHER: Zhongguo Yiyao Gongye Zazhi Bianjibu
DOCUMENT TYPE: Journal
LANGUAGE: Chinese
OTHER SOURCE(S): CASREACT 138:55697

AB Disodium combretastatin A-4 3'-O-phosphate, a potent cancer growth and tubulin assembly inhibitor, was successfully synthesized via Wittig reaction between phosphonium bromide precedingly synthesized from 3,4,5-trimethoxybenzyl alc. and silyl ether of isovanillin, desilylation, phosphorylation, cleavage of the phosphate ester, and salt formation in an overall yield of 32%.

IT **117048-59-6P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(synthesis of disodium combretastatin A-4 3'-O-phosphate)

RN 117048-59-6 CAPLUS
CN Phenol, 2-methoxy-5-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



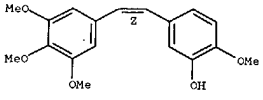
L24 ANSWER 42 OF 157 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2002:112627 CAPLUS
DOCUMENT NUMBER: 136:303544
TITLE: Protease-mediated fragmentation of p-amidobenzyl ethers: A new strategy for the activation of anticancer prodrugs
AUTHOR(S): Toki, Brian E.; Cerveny, Charles G.; Wahl, Alan F.; Senter, Peter D.
CORPORATE SOURCE: Seattle Genetics, Bothell, WA, 98021, USA
SOURCE: Journal of Organic Chemistry (2002), 67(6), 1866-1872
CODEN: JOCEAH; ISSN: 0022-3263
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English

AB A new anticancer prodrug activation strategy based on the 1,6-elimination reaction of p-aminobenzyl ethers is described. Model studies were undertaken with the N-protected peptide benzyloxycarbonyl-valine-citrulline (Z-val-cit), which was attached to the amino groups of p-aminobenzyl ether derivs. of 1-naphthol and N-acetylnorephedrine. The amide bond that formed was designed for hydrolysis by cathepsin B, a protease assocd. with rapidly growing and metastatic carcinomas. Upon treatment with the enzyme, the Z-val-cit-p-amidobenzyl ether of 1-naphthol underwent peptide bond hydrolysis with the rapid release of 1-naphthol. The aliph. Z-val-cit-p-amidobenzyl ether of N-acetylnorephedrine also underwent amide bond hydrolysis, but without the ensuing elimination of N-acetylnorephedrine. On the basis of these results, the phenolic anticancer drugs etoposide and combretastatin A-4 were attached to the Z-val-cit-p-amidobenzyl alc. through ether linkages, forming the peptide-drug derivs. Both compds. were stable in aq. buffers and serum and underwent ether fragmentation upon treatment with cathepsin B, resulting in the release of the parent drugs in chem. unmodified forms. The released drugs were 13-50 times more potent than were the prodrug precursors on a panel of cancer cell lines. In contrast, the corresponding carbonate deriv. of combretastatin A-4 was unstable in aq. environments and was as cytotoxic as combretastatin A-4. This result extends the use of the self-immolative p-aminobenzyl group for the fragmentation of arom. ethers and provides a new strategy for anticancer prodrug development.

IT **117048-59-6**, Combretastatin A-4
RL: RCT (Reactant); RACT (Reactant or reagent)
(protease-mediated fragmentation of p-amidobenzyl ethers: strategy for activation of anticancer prodrugs)

RN 117048-59-6 CAPLUS
CN Phenol, 2-methoxy-5-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



REFERENCE COUNT: 42 THERE ARE 42 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

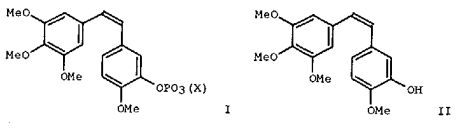
L24 ANSWER 43 OF 157 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2002:72094 CAPLUS
DOCUMENT NUMBER: 136:134622
TITLE: Methods of synthesizing prodrugs of combretastatin A-4
INVENTOR(S): Seyedi, Faye; Gale, Jonathan; Haider, Reem; Hoare, John
PATENT ASSIGNEE(S): Oxigene, Inc., USA
SOURCE: PCT Int. Appl., 41 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002006279	A1	20020124	WO 2001-US22403	20010717
WO 2002006279	C1	20020418		
WO 2002006279	C2	20030403		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

US 2002119951	A1	20020829	US 2001-908321	20010717

PRIORITY APPLN. INFO.: US 2000-218766P P 20000717
OTHER SOURCE(S): CASREACT 136:134622
GI

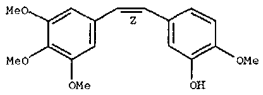


AB The present invention discloses improved methods of synthesizing a phosphate ester of combretastatin A-4, such as I [X = HZ1, Z2; Z1 = Na+, Li+; Z2 = Mg+2, Zn+2, Ca+2, Cs+2, imidazole, morpholine, etc.], and trans-isomers thereof. Thus, combretastatin A-4 (II) is reacted with dibenzylphosphite in the presence of carbon tetrabromide, or with 2,2,2-trichloroethyl phosphorodichloridate, to form a phosphate ester of combretastatin A-4 with protecting groups thereon.

IT **117048-59-6P**, Combretastatin A-4
RL: PAC (Pharmacological activity); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(methods of synthesizing prodrugs of combretastatin A-4)

RN 117048-59-6 CAPLUS
CN Phenol, 2-methoxy-5-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

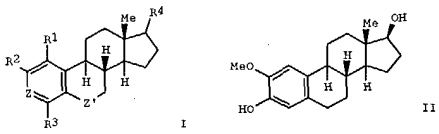
L24 ANSWER 43 OF 157 CAPLUS COPYRIGHT 2003 ACS (Continued)
Double bond geometry as shown.



L24 ANSWER 44 OF 157 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2002:11127 CAPLUS
DOCUMENT NUMBER: 136:64669
TITLE: Estrogenic compounds as antiangiogenic agents
INVENTOR(S): D'Amato, Robert J.; Varma, Ravi K.; Haugwitz, Rudiger G.; Cushman, Mark
PATENT ASSIGNEE(S): USA
SOURCE: U.S. Pat. Appl. Publ., 14 pp., Cont. of U.S. Ser. No. 154,322, abandoned.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2002002294	A1	20020103	US 2001-899702	20010705
PRIORITY APPLN. INFO.:			US 1997-59916P P	19970924
			US 1998-154322 B1	19980916

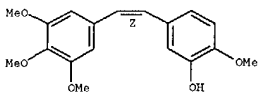
OTHER SOURCE(S): MARPAT 136:64669
GI



AB 2-Methoxyestradiol derivs., such as I [R1, R3 = H, Cl, Br, I, F, CN, alkyl, OH, CH2OH, NH2, alkylamino; R2 = N3, CN, C.tplbond.CR, C:CHR, RCH:CH2, C.tplbond.CH, OR, R-R1, OR-R1 (R = alkyl, R1 = OH, NH2, Cl, Br, I, F, CF3); Z = CH, COH, CR2-OH (R2 = alkyl, aralkyl); Z' = CH2, CO, CH(OH); C:NOH, C:NOR5, CHC.tplbond.N, CHNR5R5 (R5 = H, alkyl, aralkyl)], were used for treating mammalian disease characterized by undesirable angiogenesis. Thus, 2-methoxyestradiol (II) showed inhibition of tubulin polymn. (IC50 = 3.6.+-.0.4 .mu.M), inhibition of colchicine binding to tubulin (1.9.+-.0.2 .mu.M) and antitumor activity against breast, CNS, melanoma, ovarian tumor cell assay in vitro.
IT **117048-59-6**, Combretastatin A-4
RL: ADV (Adverse effect, including toxicity); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(estrogenic compds. as antiangiogenic agents)
RN 117048-59-6 CAPLUS
CN Phenol, 2-methoxy-5-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

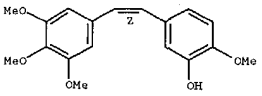
Double bond geometry as shown.

L24 ANSWER 44 OF 157 CAPLUS COPYRIGHT 2003 ACS (Continued)



L24 ANSWER 45 OF 157 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2002:9419 CAPLUS
DOCUMENT NUMBER: 136:272793
TITLE: Combination bacteriolytic therapy for the treatment of experimental tumors
AUTHOR(S): Dang, Long H.; Bettegowda, Chetan; Huso, David L.; Kinzler, Kenneth W.; Vogelstein, Bert
CORPORATE SOURCE: The Howard Hughes Medical Institute, Program in Cellular and Molecular Medicine, Division of Comparative Medicine, The Johns Hopkins School of Medicine, Baltimore, MD, 21231, USA
SOURCE: Proceedings of the National Academy of Sciences of the United States of America (2001), 98(26), 15155-15160
CODEN: PNASA6; ISSN: 0027-8424
PUBLISHER: National Academy of Sciences
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Current chemotherapeutic approaches for cancer are in part limited by the inability of drugs to destroy neoplastic cells within poorly vascularized compartments of tumors. We have here systematically assessed anaerobic bacteria for their capacity to grow expansively within avascular compartments of transplanted tumors. Among 26 different strains tested, one (Clostridium novyi) appeared particularly promising. We created a strain of C. novyi devoid of its lethal toxin (C. novyi-NT) and showed that i.v. injected C. novyi-NT spores germinated within the avascular regions of tumors in mice and destroyed surrounding viable tumor cells. When C. novyi-NT spores were administered together with conventional chemotherapeutic drugs, extensive hemorrhagic necrosis of tumors often developed within 24 h, resulting in significant and prolonged antitumor effects. This strategy, called combination bacteriolytic therapy (COBALT), has the potential to add a new dimension to the treatment of cancer.
IT **117048-59-6**, Combretastatin A4
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(combination antitumor therapy with toxin-devoid anaerobic bacteria spores and chemotherapeutic agents)
RN 117048-59-6 CAPLUS
CN Phenol, 2-methoxy-5-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

Double bond geometry as shown.

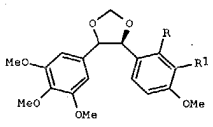


L24 ANSWER 46 OF 157 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2001:832999 CAPLUS
DOCUMENT NUMBER: 135:366721
TITLE: Antitubulin assembly and cell growth inhibitor denominated "dioxostatin"
INVENTOR(S): Pettit, George R.; Lippert, John W., III
PATENT ASSIGNEE(S): Arizona Board of Regents, Arizona State University, USA
SOURCE: PCT Int. Appl., 38 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001084929	A1	20011115	WO 2001-US14790	20010508
W: CA, JP, US				
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR				
EP 1283672	A1	20030219	EP 2001-935147	20010508
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI, CY, TR				

PRIORITY APPLN. INFO.: US 2000-202770P P 20000509
WO 2001-US14790 W 20010508

GI



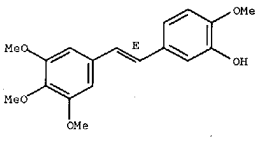
I

AB A new inhibitor of microtubule assembly (IC50 0.59 .mu.M); with antineoplastic properties, denominated "dioxostatin", has been synthesized and its effectiveness against human cancer and murine P388 lymphocytic leukemia cell lines demonstrated. Dioxostatin has the following structure (I).

IT **109971-63-3**, Combretastatin A-1 **109984-84-1**
117048-59-6, Combretastatin A-4 **117048-62-1**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(antitubulin assembly and cell growth inhibitor denominated dioxostatin in relation to antineoplastic and antimicrobial activity)

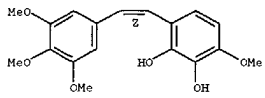
RN 109971-63-3 CAPLUS
CN 1,2-Benzenediol, 3-methoxy-6-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

L24 ANSWER 46 OF 157 CAPLUS COPYRIGHT 2003 ACS (Continued)



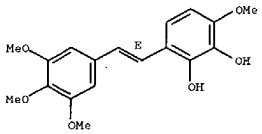
REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L24 ANSWER 46 OF 157 CAPLUS COPYRIGHT 2003 ACS (Continued)
Double bond geometry as shown.



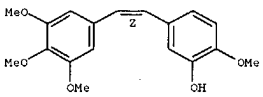
RN 109984-84-1 CAPLUS
CN 1,2-Benzenediol, 3-methoxy-6-[(1E)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



RN 117048-59-6 CAPLUS
CN Phenol, 2-methoxy-5-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



RN 117048-62-1 CAPLUS
CN Phenol, 2-methoxy-5-[(1E)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

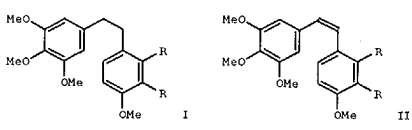
Double bond geometry as shown.

L24 ANSWER 47 OF 157 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2001:798232 CAPLUS
DOCUMENT NUMBER: 135:344595
TITLE: Preparation of combretastatin A-1 phosphate and combretastatin B-1 phosphate prodrugs with increased solubility
INVENTOR(S): Pettit, George R.; Lippert, John W., III
PATENT ASSIGNEE(S): Arizona Board of Regents, A Body Corporate of the State of Arizona, Acting for and On Behalf of Arizona State University, USA
SOURCE: PCT Int. Appl., 41 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001081355	A1	20011101	WO 2001-US13858	20010427
W: CA, JP, US				
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR				
EP 1278758	A1	20030129	EP 2001-928978	20010427
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI, CY, TR				

PRIORITY APPLN. INFO.: US 2000-200395P P 20000427
WO 2001-US13858 W 20010427
OTHER SOURCE(S): CASREACT 135:344595

GI



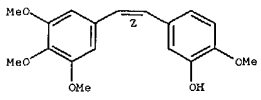
I II

AB The present invention relates to the syntheses and structural elucidation of Combretastatin A1-Phosphate Prodrugs and Combretastatin B1-Phosphate Prodrugs and the use of those prodrugs in the treatment of neoplastic diseases. The prodrugs described herein have the structure: Combretastatin A-1 Phosphate Prodrug (I; R = P(O)(ONa)2, OPO3Z (e.g. Z = Li2, Ca, (morpholinium)2, (papaverinium)2); ED50 < 0.0100 .mu.g/mL, P388 cell line for R = OPO3Na2) and Combretastatin B-1 Phosphate Prodrug (II; ED50 0.335 .mu.g/mL, P388 cell line for R = OPO3Na2). Although no methods of prepn. are claimed, the original synthesis of combretastatin A-1 was improved to allow an efficient scale-up procedure and procedures for diphosphorylation of combretastatin A-1 followed by conversions to various phosphate salts of combretastatin A-1 and its reduced form are described. Soly. and cancer cell line results are tabulated for many of the claimed compds.

IT **117048-59-6**, Combretastatin A-4
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(comparison of antitumor activity of combretastatin A-1 phosphate and

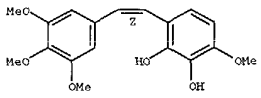
L24 ANSWER 47 OF 157 CAPLUS COPYRIGHT 2003 ACS (Continued)
combretastatin B-1 phosphate prodrugs to that of)
RN 117048-59-6 CAPLUS
CN Phenol, 2-methoxy-5-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



IT **109971-63-3P**, Combretastatin A-1
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); IMF (Industrial manufacture); RCT (Reactant); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent)
(prepn. and conversion to phosphate prodrugs with increased soly. and comparison of antitumor activity of combretastatin A-1 phosphate and combretastatin B-1 phosphate prodrugs to that of)
RN 109971-63-3 CAPLUS
CN 1,2-Benzenediol, 3-methoxy-6-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

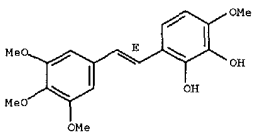
Double bond geometry as shown.



IT **109984-84-1P**, (E)-2-(2,3-Dihydroxy-4-methoxyphenyl)-1-(3,4,5-trimethoxyphenyl)ethene
RL: SPN (Synthetic preparation); PREP (Preparation)
(prepn. of)
RN 109984-84-1 CAPLUS
CN 1,2-Benzenediol, 3-methoxy-6-[(1E)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

Double bond geometry as shown.

L24 ANSWER 47 OF 157 CAPLUS COPYRIGHT 2003 ACS (Continued)

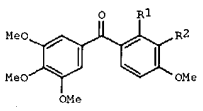


REFERENCE COUNT: 11 THERE ARE 11 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L24 ANSWER 48 OF 157 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2001:798176 CAPLUS
DOCUMENT NUMBER: 135:331299
TITLE: Synthesis of hydroxyphenstatin and the prodrugs thereof as anticancer and antimicrobial agents
INVENTOR(S): Pettit, George R.; Grealish, Matthew P.
PATENT ASSIGNEE(S): Arizona Board of Regents, A Body Corporate of the State of Arizona, Acting for and On Behalf of Arizona State University, USA
SOURCE: PCT Int. Appl., 40 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001081288	A1	20011101	WO 2001-US13731	20010427
W: CA, JP, US				
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR				
EP 1299337	A1	20030409	EP 2001-930892	20010427
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI, CY, TR				

PRIORITY APPLN. INFO.: US 2000-200394P P 20000427
WO 2001-US13731 W 20010427
OTHER SOURCE(S): MARPAT 135:331299
GI

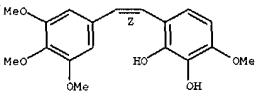


I

AB The benzophenone deriv. of combretastatin A-1, designated "hydroxyphenstatin" [I; R1 = R2 = OH] and X-hydroxypenstatin diphosphate wherein X is selected from Na, Ca, Li and K in a pharmaceutically acceptable carrier, were prepd. for use as anticancer and antimicrobial agents. Thus, I [R1 = R2 = OPO(ONa)2 (II)] was prepd. via a multistep synthetic sequence starting from 3,4,5-trimethoxy benzaldehyde, o-vanillin, dibenzylphosphite and sodium iodide. The prepd. hydroxyphenstatin derivs. were tested for antitumor activity against a series of human cancer cells and murine P388 lymphocytic leukemia, antibacterial and antifungal activities (II GI50 = 0.0336 .mu.g/mL vs P388 cell line; IC50= >40 .mu.M inhibition of tubulin polymn.; I [R1 = R2 = OPO(OCH2Ph)2] MIC = 50-100 .mu.g/dish).
IT **109971-63-3**, Combretastatin A-1 **117048-59-6**, Combretastatin A-4
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(inhibition of tubulin polymn. and inhibition of colchicine binding)
RN 109971-63-3 CAPLUS

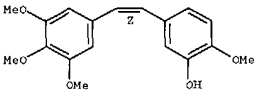
L24 ANSWER 48 OF 157 CAPLUS COPYRIGHT 2003 ACS (Continued)
CN 1,2-Benzenediol, 3-methoxy-6-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



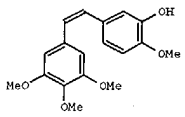
RN 117048-59-6 CAPLUS
CN Phenol, 2-methoxy-5-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L24 ANSWER 49 OF 157 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2001:795470 CAPLUS
DOCUMENT NUMBER: 136:102221
TITLE: Novel Syntheses of Cis and Trans Isomers of Combretastatin A-4
AUTHOR(S): Gaukroger, Keira; Hadfield, John A.; Hepworth, Lucy A.; Lawrence, Nicholas J.; McGown, Alan T.
CORPORATE SOURCE: CRC Drug Development Group and CRC Radiochemical Targeting and Imaging Group, Paterson Institute for Cancer Research Christie Hospital NHS Trust, Manchester, M20 4BX, UK
SOURCE: Journal of Organic Chemistry (2001), 66(24), 8135-8138
CODEN: JOCEAH; ISSN: 0022-3263
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 136:102221
GI



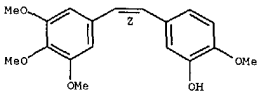
I

AB A high-yielding, two-step stereoselective synthesis of the anticancer drug (Z)-combretastatin A-4 (I) was devised. The method uses the Perkin condensation of 3,4,5-trimethoxyphenylacetic acid and 3-hydroxy-4-methoxybenzaldehyde followed by decarboxylation of the cinnamic acid intermediate using copper and quinoline. The iodine-catalyzed isomerization of the Z isomer I results in complete conversion to the E isomer. The Suzuki cross-coupling of an aryl boronic acid and vinyl bromide has also been successfully employed to produce both Z and E isomers of combretastatin A-4 stereoselectively. Both methods are far superior to the current five-step Wittig synthesis in which both isomers are produced nonstereoselectively.

IT **117048-59-5P**, Combretastatin A-4
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(synthesis of cis and trans isomers of combretastatin A-4)
RN 117048-59-6 CAPLUS
CN Phenol, 2-methoxy-5-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

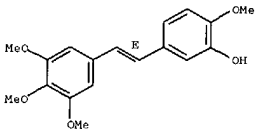
Double bond geometry as shown.

L24 ANSWER 49 OF 157 CAPLUS COPYRIGHT 2003 ACS (Continued)



IT **117048-62-1P**, Trans-combretastatin A-4
RL: SPN (Synthetic preparation); PREP (Preparation)
(synthesis of cis and trans isomers of combretastatin A-4)
RN 117048-62-1 CAPLUS
CN Phenol, 2-methoxy-5-[(1E)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



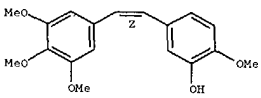
REFERENCE COUNT: 46 THERE ARE 46 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L24 ANSWER 50 OF 157 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2001:750594 CAPLUS
DOCUMENT NUMBER: 136:395459
TITLE: Potent anti-metastatic activity of combretastatin-A4
AUTHOR(S): Griggs, Jeremy; Brindle, Kevin M.; Metcalfe, James C.; Hill, Sally A.; Smith, Gerry A.; Beauregard, Daniel A.; Hesketh, Robin
CORPORATE SOURCE: Department of Biochemistry, University of Cambridge, Cambridge, CB2 1QW, UK
SOURCE: International Journal of Oncology (2001), 19(4), 821-825
CODEN: IJONES; ISSN: 1019-6439
PUBLISHER: International Journal of Oncology
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The requirement for tumor vascularization to permit the expansion of solid tumors beyond a threshold size of approx. 1 mm diam. has focussed attention on anti-vascular and anti-angiogenic agents for cancer therapy. Combretastatin-A4 (cis-CA-4P) is a tubulin-binding agent that is cytotoxic for proliferating endothelial cells in vitro and causes anti-vascular effects in the established tumor vessels of some primary tumors. Preliminary data from Phase I clin. trials indicate that cis CA-4 may also be effective in targeting the vasculature of human tumors. As metastatic disease is the principal cause of mortality in cancer, we have investigated the effects of cis CA-4 on metastatic development using an in vivo model. We show that bolus or continuous administration of cis CA-4P results in potent inhibition of metastases derived from ectopic primary Lewis lung carcinomas in mice whereas the trans CA-4 isomer is without effect. These data further characterize the activity of CA-4 in vivo and suggest that the drug should be evaluated clin. as an anti-metastatic agent.

IT **117048-59-6**, Combretastatin-A4 **117048-62-1**, trans-Combretastatin-A4
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(anti-metastatic activity of combretastatin-A4)
RN 117048-59-6 CAPLUS
CN Phenol, 2-methoxy-5-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

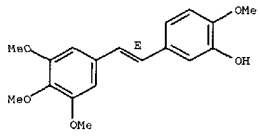
Double bond geometry as shown.



RN 117048-62-1 CAPLUS
CN Phenol, 2-methoxy-5-[(1E)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

Double bond geometry as shown.

L24 ANSWER 50 OF 157 CAPLUS COPYRIGHT 2003 ACS (Continued)



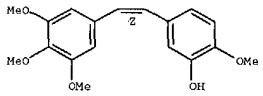
REFERENCE COUNT: 21 THERE ARE 21 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L24 ANSWER 51 OF 157 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2001:628999 CAPLUS
DOCUMENT NUMBER: 135:344335
TITLE: The synthesis and tubulin binding activity of thiophene-based analogues of combretastatin A-4
AUTHOR(S): Flynn, B. L.; Flynn, G. P.; Hamel, E.; Jung, M. K.
CORPORATE SOURCE: The Faculties, Department of Chemistry, Australian National University, Canberra, 0200, Australia
SOURCE: Bioorganic & Medicinal Chemistry Letters (2001), 11(17), 2341-2343
CODEN: BMCLE8; ISSN: 0960-894X
PUBLISHER: Elsevier Science Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB A no. of analogs of combretastatin A-4, contg. a thiophene ring interposed between the two Ph groups, have been prepd. The synthesis of these compds. employed a combination of palladium-mediated coupling and iodocyclization techniques. The thiophene compds. I, II (R1,R2,R3,R5 = OMe; R4 = OH, R6 = H; X = O), II (R1 = OH, R2,R4,R5,R6 = OMe; R3 = OH; X = OH, H), and II (R1 = OH, R2,R4,R5,R6 = OMe; R3 = OH; X = O) also represent non-benzofused analogs of some recently described tubulin binding benzo[b]thiophenes. The most active thiophene compds. identified in this study were I, II (R1,R2,R3,R5 = OMe; R4 = OH, R6 = H; X = O), and II (R1 = OH, R2,R4,R5,R6 = OMe; R3 = OH; X = OH, H). Overall they are less active than combretastatin A-4 but exhibit comparable activity to the most active of the benzo[b]thiophenes. A structure-activity relationship of these compds. is considered.
IT **117048-59-6**, Combretastatin A-4
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(synthesis and tubulin binding activity of thiophene-based analogs of combretastatin A-4)
RN 117048-59-6 CAPLUS
CN Phenol, 2-methoxy-5-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

Double bond geometry as shown.

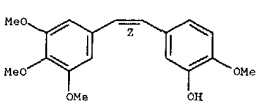


REFERENCE COUNT: 23 THERE ARE 23 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L24 ANSWER 51 OF 157 CAPLUS COPYRIGHT 2003 ACS (Continued)

L24 ANSWER 52 OF 157 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2001:483533 CAPLUS
DOCUMENT NUMBER: 136:318885
TITLE: Combretastatin A-4 and hyperthermia; a potent combination for the treatment of solid tumors
AUTHOR(S): Eikesdal, H. P.; Bjerkvig, R.; Mella, O.; Dahl, O.
CORPORATE SOURCE: Haukeland University Hospital, Department of Oncology, University of Bergen, Bergen, 5021, Norway
SOURCE: Radiotherapy and Oncology (2001), 60(2), 147-154
CODEN: RAONDT; ISSN: 0167-8140
PUBLISHER: Elsevier Science Ireland Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Attacking tumor vasculature is a promising approach for the treatment of solid tumors. The tubulin inhibitor combretastatin A-4 disodium phosphate (CA-4) is a new vascular targeting drug which displays a low toxicity profile. We wanted to investigate how CA-4 influences tumor perfusion in the BT4An rat glioma and how the vascular targeting properties of CA-4 could be exploited to augment hyperthermic damage towards tumor vasculature. We used the 86RbCl extn. technique to assess how CA-4 influences tumor perfusion, and the tumor endothelium was exam. for morphol. changes induced by the drug. We combined CA-4 (50 mg/kg i.p.) with hyperthermia (44, 60 min) at different time intervals to evaluate how therapy should be designed to affect tumor growth, and we studied the tumors histol. to assess tissue viability. We found that CA-4 induced a profound, but transient redn. in tumor perfusion 3-6 h postinjection. If hyperthermia was administered 3-6 h after injecting CA-4, massive hemorrhagic necrosis developed, and tumor response was significantly enhanced compared to simultaneous administration of the two treatment modalities (P<0.005). CA-4 alone had no influence on tumor growth and failed to disrupt the vasculature of the BT4An solid tumors. Interestingly though, a mild endothelial edema was obsd. in some tumor areas 3 h after injecting CA-4. We conclude that the combination of CA-4 and hyperthermia is a potent therapeutic option for BT4An tumors, but the selection of adequate time intervals between CA-4 and hyperthermia are imperative to obtain tumor response.
IT **117048-59-6**, Combretastatin A-4
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(combretastatin A-4 and hyperthermia combination for treatment of solid tumors)
RN 117048-59-6 CAPLUS
CN Phenol, 2-methoxy-5-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

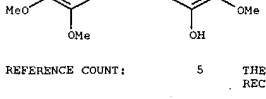
Double bond geometry as shown.



REFERENCE COUNT: 34 THERE ARE 34 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L24 ANSWER 53 OF 157 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2001:379423 CAPLUS
DOCUMENT NUMBER: 135:189977
TITLE: Specific targeting of cytosine deaminase to solid tumors by engineered Clostridium acetobutylicum
AUTHOR(S): Theys, Jan; Landuyt, Willy; Nuyts, Sandra; Van Mellaert, Lieve; Van Oosterom, Allan; Lambin, Philippe; Anne, Jozef
CORPORATE SOURCE: Laboratory of Bacteriology, Rega Institute for Medical Research, Louvain, B-3000, Belg.
SOURCE: Cancer Gene Therapy (2001), 8(4), 294-297
CODEN: CGTHEG; ISSN: 0929-1903
PUBLISHER: Nature America Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The presence of severe hypoxia and necrosis in solid tumors offers the potential to apply an anaerobic bacterial enzyme/prodrug approach in cancer treatment. In this context the apathogenic C. acetobutylicum was genetically engineered to express and secrete E. coli cytosine deaminase (CDase). Considerable levels of functional cytosine deaminase were detected in lysates and supernatants of recombinant C acetobutylicum cultures. After administration of the recombinant Clostridium to rhabdomyosarcoma bearing rats used as a model, cytosine deaminase could be detected at the tumor site. Moreover, following administration of the vascular targeting agent combretastatin A-4 phosphate significantly increased levels of cytosine deaminase were detected at the tumor site as a consequence of enlarged tumor necrosis and subsequently improved growth of C. acetobutylicum. The results provide evidence for the potential application of Clostridium-based therapeutic protein transfer to tumors in anticancer therapy.
IT **117048-59-6**, Combretastatin A4
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(targeting of cytosine deaminase to solid tumors by engineered Clostridium acetobutylicum)
RN 117048-59-6 CAPLUS
CN Phenol, 2-methoxy-5-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

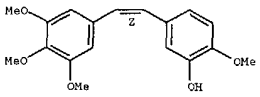
L24 ANSWER 54 OF 157 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2001:363661 CAPLUS
DOCUMENT NUMBER: 136:31366
TITLE: Combretastatin A4 prodrug study of effect on the growth and the microvasculature of colorectal liver metastases in a murine model
AUTHOR(S): Malcontenti-Wilson, Cathy; Muralidharan, Vijayaragavan; Skinner, Stewart; Christophi, Chris; Sherris, David; O'Brien, Paul E.
CORPORATE SOURCE: Alfred Hospital, Monash University Department of *Surgery*, Melbourne, 3181, Australia
SOURCE: Clinical Cancer Research (2001), 7(4), 1052-1060
CODEN: CCREF4; ISSN: 1078-0432
PUBLISHER: American Association for Cancer Research
DOCUMENT TYPE: Journal
LANGUAGE: *English*

AB Combretastatin A4P (CA4P) is a prodrug that, in active form, binds to tubulin microtubules of capillary endothelial cells. Studies to date indicate it has significant activity as a specific tumor vascular targeting agent. The goals were to assess the effects of CA4P on tumor growth and microvasculature of colorectal liver metastases in the mouse model, using stereol. and histol. methods to measure tumor growth, and vascular corrosion casting and laser doppler flowmetry to assess effect on the microvasculature. Continuous s.c. infusion of CA4P produced a major redn. in tumor growth. The percentage of the liver occupied by metastases decreased from 20.55.+-.13.3% in controls to 7.46.+-.5.99% in treated animals (P = 0.03). Ultrastructural study of tumor microvasculature after a single dose of CA4P revealed marked effects 1 h after treatment. There was loss of patent microvessels at the normal liver-tumor interface. Central microvascular d. was reduced, with constriction and tapering of vessels. CA4P appeared to cause no damage to normal liver tissue or vasculature. Tumor blood flow decreased from 37.6.+-.13.9% in controls to 24.4.+-.6.1% in tumors >5 mm in diam., 1 h after treatment with CA4P (P < 0.03). Quant. histol. of tissue at 6 and 24 h after CA4P treatment showed a significant increase in tumor necrosis (48,7.+-.21% and 55.5.+-.19% compared with controls, 20.6.+-.8%; P = 0.01). Continuous infusion with *CA4P causes marked redn. in tumor vol. A single dose of CA4P causes major* changes of the tumor microvasculature, redn. of tumor blood flow, and increase in tumor necrosis. CA4P has a potential role in the management of patients with liver metastases.

IT **117048-59-6**, Combretastatin A4
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(combretastatin A4 prodrug study of effect on the growth and the microvasculature of colorectal liver metastases in a murine model)
RN 117048-59-6 CAPLUS
CN Phenol, 2-methoxy-5-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

Double bond geometry as shown.

L24 ANSWER 54 OF 157 CAPLUS COPYRIGHT 2003 ACS (Continued)



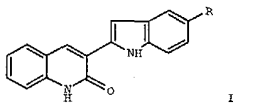
REFERENCE COUNT: 21 THERE ARE 21 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L24 ANSWER 55 OF 157 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2001:300706 CAPLUS
DOCUMENT NUMBER: 134:326411
TITLE: Preparation of 3-(2-indolyl)quinoline-2-one derivatives as tyrosine kinase inhibitors
INVENTOR(S): Arrington, Kenneth L.; Bilodeau, Mark T.; Fraley, Mark E.; Hartman, George D.; Hoffman, William F.; Hungate, Randall W.; Kim, Yuntae
PATENT ASSIGNEE(S): Merck & Co., Inc., USA
SOURCE: PCT Int. Appl., 130 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001029025	A2	20010426	WO 2000-US28625	20001016
WO 2001029025	A3	*20011101*		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, *SE, SG, SI, SK, SL, TJ, TM*, TR, TT, TZ, UA, *UG, US*, UZ, VN, *YU*, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
BR 2000014843	A	20020611	BR 2000-14843	20001016
EP 1226136	A2	20020731	EP 2000-978230	20001016
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL				
JP 2003512369	T2	20030402	JP 2001-531825	20001016
US 6306874	B1	20011023	US 2000-690598	20001017
NO 2002001820	A	20020523	NO 2002-1820	20020418
BG 106710	A	20030331	BG 2002-106710	20020516

PRIORITY APPLN. INFO.: US 1999-160356P P 19991019
WO 2000-US28625 W 20001016
OTHER SOURCE(S): MARPAT 134:326411
GI

L24 ANSWER 55 OF 157 CAPLUS COPYRIGHT 2003 ACS (Continued)



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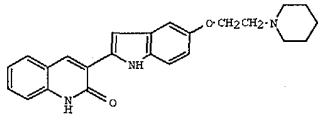
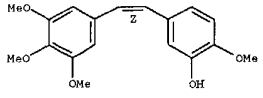


II

AB Title compds. [I; R = (CH3)2NCH2CH(CH3)CH2O, (CH3OCH2CH2)(C6H5CH2)NCH2CH2O, (CH3CH2)2NCH2CH2O, (CH3)(C6H5CH2)NCH2CH2CH2O, *(CH3OCH2CH2)(HOOCCH2CH2)NCH2CH2O, (CH3OCH2CH2)(CH3SO2)NCH2*, cycloalkylaminoalkyl, heterocyclylalkyl, etc.], stereoisomer, and pharmaceutically acceptable salts are prepd. and inhibit, regulate and/or modulate tyrosine kinase signal transduction. Title compds. are tested on VEGF-stimulated mitogenesis of human vascular endothelial cells in culture with IC50 *values between* 0.001-5.0 *.mu.M. Pharmaceutical compns. and* methods of using them to treat tyrosine kinase-dependent diseases and conditions, such as angiogenesis, cancer, tumor growth, atherosclerosis, age related macular degeneration, diabetic retinopathy, inflammatory diseases, etc. are discussed. Thus, the title compd. II was prepd.

IT **117048-59-6**, Combretastatin A-4
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(prepn. of 3-(2-indolyl)quinoline-2-one derivs. as tyrosine kinase inhibitors in compn. with other agents)
RN 117048-59-6 CAPLUS
CN Phenol, 2-methoxy-5-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



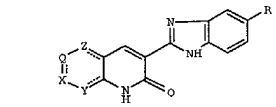
L24 ANSWER 56 OF 157 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2001:300674 CAPLUS
DOCUMENT NUMBER: 134:326527
TITLE: Preparation of benzimidazole derivatives as tyrosine kinase inhibitors
INVENTOR(S): Fraley, Mark E.; Hambaugh, Scott R.; Hungate, Randall W.
PATENT ASSIGNEE(S): Merck & Co. Inc., USA
SOURCE: PCT Int. Appl., 107 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001028993	A2	20010426	WO 2000-US28641	20001016
WO 2001028993	A3	20010913		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
AU 2001010913	A5	20010430	AU 2001-10913	20001016
EP 1226119	A2	20020731	EP 2000-972217	20001016
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL				
JP 2003512353	T2	20030402	JP 2001-531793	20001016
US 6479512	B1	20021112	US 2000-690602	20001017

PRIORITY APPLN. INFO.: US 1999-160362P P 19991019
WO 2000-US28641 W 20001016

OTHER SOURCE(S): MARPAT 134:326527
GI

L24 ANSWER 56 OF 157 CAPLUS COPYRIGHT 2003 ACS (Continued)



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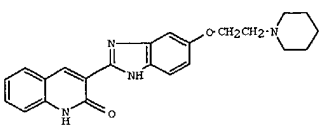


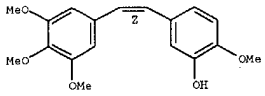
II

AB Title compds. {I; X = CH, N; Y = CH, N, S; Z = CH, S, electron pair; Q = CH, electron pair; dotted bond = single, double; R = (CH3)2NCH2CH(CH3)CH2O, (CH3OCH2CH2)(C6H5CH2)NCH2CH2O, (CH3CH2)2NCH2CH2O, (CH3)(C6H5CH2)NCH2CH2CH2O, (CH3OCH2CH2)(HOOCCH2CH2)NCH2CH2O, (CH3OCH2CH2)(CH3SO2)NCH2, cycloalkylaminoalkyl, heterocyclylalkyl, etc.], stereoisomer, and pharmaceutically acceptable salts are prepd. and inhibit, regulate and/or modulate tyrosine kinase signal transduction. Title compds. are tested on VEGF-stimulated mitogenesis of human vascular endothelial cells in culture with IC50 values between 0.001-5.0 .mu.M. Pharmaceutical compns. and methods of using them to treat tyrosine kinase-dependent diseases and conditions, such as angiogenesis, cancer, tumor growth, atherosclerosis, age related macular degeneration, diabetic retinopathy, inflammatory diseases, etc. are discussed. Thus, the title compd. II was prepd.

IT **117048-59-6**, Combretastatin A-4
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(prepn. of benzimidazole derivs. as tyrosine kinase inhibitors)

RN 117048-59-6 CAPLUS
CN Phenol, 2-methoxy-5-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



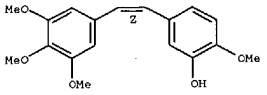
L24 ANSWER 57 OF 157 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2001:294493 CAPLUS
DOCUMENT NUMBER: 135:220760
TITLE: Effects of combretastatin A4 phosphate on endothelial cell morphology in vitro and relationship to tumor vascular targeting activity in vivo
AUTHOR(S): Galbraith, Susan M.; Chaplin, David J.; Lee, Francesca; Stratford, Michael R. L.; Locke, Rosalind J.; Vojnovic, Borivoj; Tozer, Gillian M.
CORPORATE SOURCE: Tumour Microcirculation Group, Gray Laboratory Cancer Research Trust, Northwood, HA6 2JR, UK
SOURCE: Anticancer Research (2001), 21(1A), 93-102
CODEN: ANTRD4; ISSN: 0250-7005
PUBLISHER: International Institute of Anticancer Research
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Combretastatin A4 Phosphate (CA4P) is a tubulin binding agent which causes rapid tumor vascular shutdown. It has anti-proliferative and apoptotic effects on dividing endothelial cells after prolonged exposure, but these effects occur on a much longer time scale than the redn. in tumor blood flow. This study compared the time course of CA4P effects on endothelial cell shape and redn. in red cell velocity. Endothelial cell area and form factor (1 - 4.PI. .times. area .times. perimeter-2) were measured for proliferating and confluent HUVECs after CA4P treatment. Recovery of shape after CA4P and colchicine was compared. Window chamber studies of tumors were used to measure red cell velocity. 70% Redn. in red cell velocity and 44% redn. in HUVEC form factor occurred by 10 min. Proliferating HUVECs underwent greater cell shape change after CA4P, which occurred at lower doses than for confluent cells. Cell shape recovered 24 h after 30 min exposure to CA4P, but not after colchicine. The similar time course of cell shape change and red cell velocity redn. suggests endothelial cell shape change may be involved early in the in vivo events leading to vascular shutdown. Differences in the recovery from the shape changes induced by CA4P and colchicine could underlie the different toxicity profiles of these drugs.

IT **117048-59-6**, combretastatin A4
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(effects of combretastatin A4 phosphate on endothelial cell morphol. in vitro and relationship to tumor vascular targeting activity in vivo)

RN 117048-59-6 CAPLUS
CN Phenol, 2-methoxy-5-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



REFERENCE COUNT: 42 THERE ARE 42 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

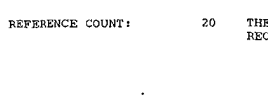
L24 ANSWER 58 OF 157 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2001:246309 CAPLUS
DOCUMENT NUMBER: 135:33404
TITLE: Novel sulfonate analogues of combretastatin A-4: potent antimitotic agents
AUTHOR(S): Gwaltney, S. L.; Imade, H. M.; Barr, K. J.; Li, Q.; Gehrke, L.; Credo, R. B.; Warner, R. B.; Lee, J. Y.; Kovar, P.; Wang, J.; Nukkala, M. A.; Zielinski, N. A.; Frost, D.; Ng, S.-C.; Sham, H. L.
CORPORATE SOURCE: D47B, Cancer Research, Abbott Laboratories, Abbott Park, IL, 60064-6101, USA
SOURCE: Bioorganic & Medicinal Chemistry Letters (2001), 11(7), 871-874
CODEN: BMCLE8; ISSN: 0960-894X
PUBLISHER: Elsevier Science Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 135:33404

AB Sulfonate analogs of combretastatin A-4 have been prepd. These compds. compete with colchicine and combretastatin A-4 for the colchicine binding site on tubulin and are potent inhibitors of tubulin polymn. and cell proliferation. Importantly, these compds. also inhibit the proliferation of P-glycoprotein pos. (+) cancer cells, which are resistant to many other antitumor agents. Sulfonate analogs of combretastatin A-4 have been prepd. These compds. bind to the colchicine binding site on tubulin and are potent inhibitors of tubulin polymn. and cell proliferation. Importantly, these compds. also inhibit the proliferation of P-glycoprotein pos. (+) cancer cells, which are resistant to many other antitumor agents.

IT **117048-59-6**, combretastatin A-4
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(prepn. of sulfonate analogs of combretastatin A-4 as potent antimitotic agents)

RN 117048-59-6 CAPLUS
CN Phenol, 2-methoxy-5-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

Double bond geometry as shown.

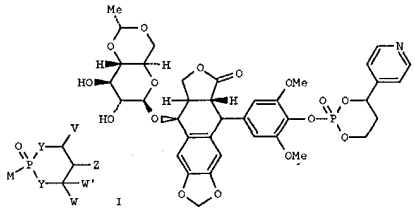


REFERENCE COUNT: 20 THERE ARE 20 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L24 ANSWER 59 OF 157 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2001:185764 CAPLUS
DOCUMENT NUMBER: 134:237345
TITLE: Preparation of prodrugs for liver specific drug delivery
INVENTOR(S): Erion, Mark D.; Reddy, K. Raja
PATENT ASSIGNEE(S): Metabasis Therapeutics, Inc., USA
SOURCE: PCT Int. Appl., 160 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001018013	A1	20010315	WO 2000-US24693	20000908
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
EP 1210354	A1	20020605	EP 2000-961694	20000908
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL				
JP 2003508539	T2	20030304	JP 2001-522236	20000908

PRIORITY APPLN. INFO.: US 1999-153128P P 19990908
WO 2000-US24693 W 20000908
OTHER SOURCE(S): MARPAT 134:237345
GI

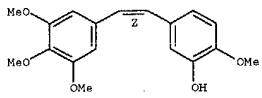


I

II

L24 ANSWER 59 OF 157 CAPLUS COPYRIGHT 2003 ACS (Continued)
AB Cyclic phosph(oramid)ate prodrugs, such as I [M = pharmaceutical agent, such as camptothecin, paclitaxel, etc.; V, W, W' = H, alkyl, arylalkyl, aryl, heteroaryl, alkenyl, alkynyl, etc.; Z = H, hydroxymethyl, acyloxymethyl, etc.; VZ or VW = fused cyclic group; Y = O, NR, etc.; R = H, alkyl, etc.], were prepd. and formulated for pharmaceutical use for the delivery of drugs. Thus, prodrug II was prepd. in 48% yield from 1-(4-pyridyl)-1,3-propanediol, POCl3, and etoposide. The prepd. prodrugs were tested for their resp. biol. activities, such as II being tested for activation in rat hepatocytes. The proposed uses of the prodrugs are to treat diseases that benefit from enhanced drug distribution to the liver and like tissues and cells that express cytochrome P 450, including hepatitis, cancer, liver fibrosis, malaria, other viral and parasitic infections, and metabolic diseases where the liver is responsible for the overprodn. of the biochem. end product, e.g. glucose (diabetes); cholesterol, fatty acids and triglycerides (hyperlipidemia) (atherosclerosis) (obesity). These prodrugs are designed to enhance oral drug delivery, to prolong pharmacodynamic half-life of the drug, to achieve sustained delivery of the parent drug, to increase the therapeutic index of the drug, and to be useful in the delivery of diagnostic imaging agents to the liver.
IT **117048-59-6**, Combretastatin A-4
RL: RCT (Reactant); THU (Therapeutic use); BIOL (Biological study); RACT (Reactant or reagent); USES (Uses)
(prepn. of prodrugs for liver specific drug delivery)
RN 117048-59-6 CAPLUS
CN Phenol, 2-methoxy-5-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

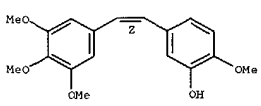
Double bond geometry as shown.



REFERENCE COUNT: 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L24 ANSWER 60 OF 157 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2001:152080 CAPLUS
DOCUMENT NUMBER: 135:146582
TITLE: Targeting tumor vasculature: The development of combretastatin A4
AUTHOR(S): Griggs, Jeremy; Metcalfe, James C.; Hesketh, Robin
CORPORATE SOURCE: Department of Biochemistry, University of Cambridge, Cambridge, CB2 1QW, UK
SOURCE: Lancet Oncology (2001), 2(2), 82-87
CODEN: LOANBN; ISSN: 1470-2045
PUBLISHER: Lancet Publishing Group
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review with 37 refs. The requirement for neovascularization to permit the development of solid tumors beyond a threshold size, has focused attention on the therapeutic potential of agents that prevent angiogenesis. The multistep nature of angiogenesis presents several targets for intervention, including the inhibition of the endothelial-cell migration or proliferation normally assocd. with developing vessels. Compds. that damage established tumor vasculature are also of potential clin. use. We review the development of one such antivascular drug, combretastatin A4. This tubulin-binding agent was originally isolated from an African shrub, Combretum caffrum. The disodium combretastatin A4 phosphate prodrug is currently undergoing phase I clin. trials in the UK and USA. This review assesses the in vitro and in vivo data for combretastatin and the prodrug, and the preliminary data that have emerged from the phase I clin. trials.
IT **117048-59-6**, combretastatin A4
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(targeting tumor vasculature: development of combretastatin A4)
RN 117048-59-6 CAPLUS
CN Phenol, 2-methoxy-5-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



REFERENCE COUNT: 37 THERE ARE 37 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L24 ANSWER 61 OF 157 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2001:137169 CAPLUS
DOCUMENT NUMBER: 134:178403
TITLE: Preparation and use of cis-stilbenes with vascular damaging activity
INVENTOR(S): Davis, Peter David
PATENT ASSIGNEE(S): Angiogene Pharmaceuticals Ltd., UK
SOURCE: PCT Int. Appl., 17 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001012579	A2	20010222	WO 2000-GB3067	20000809
WO 2001012579	A3	20011011		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
EP 1206429	A2	20020522	EP 2000-951727	20000809
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL				
JP 2003507356	T2	20030225	JP 2001-516880	20000809

PRIORITY APPLN. INFO.: GB 1999-18912 A 19990812
WO 2000-GB3067 W 20000809
OTHER SOURCE(S): MARPAT 134:178403
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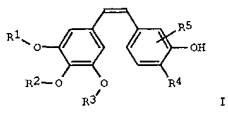

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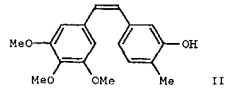


II

AB Compds. of formula I [wherein; R1, R2 and R3 are alkyl; R4 is (un)substituted alkyl, alkylthio, alkylsulfinyl, alkylsulfonyl, or halo;

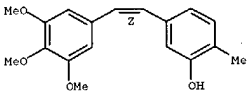
L24 ANSWER 61 OF 157 CAPLUS COPYRIGHT 2003 ACS (Continued)
R5 is H, alkoxy, alkyl, alkylthio, hydroxy or halo] are prepd. Five examples are disclosed, one of which is a dihydrogen phosphate ester prodrug. The precursor of example II was prepd. by Wittig olefination of 3,4,5-trimethoxybenzyltriphenylphosphonium bromide and 3-tert-butyldimethylsilyloxy-4-methylbenzaldehyde. Fluoride-mediated deprotection of the silyloxy intermediate provided II as a white solid. Compds. I showed activity against tumor vasculature measured by redn. in functional vascular vol. in a mouse tumor assay (CaNT tumor-bearing mice). These compds. exhibit vascular damaging activity and are therefore potentially of value in treatment of diseases where reversal of neovascularization may have therapeutic benefit.

IT **288585-59-1P**, (Z)-1-(3-Hydroxy-4-methylphenyl)-2-(3,4,5-trimethoxyphenyl)ethene
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(prepn. and use of stilbenes with vascular damaging activity)

RN 288585-59-1 CAPLUS

CN Phenol, 2-methyl-5-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

Double bond geometry as shown.

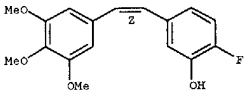


IT **326850-81-1P**, (Z)-1-(4-Fluoro-3-hydroxyphenyl)-2-(3,4,5-trimethoxyphenyl)ethene **326850-82-2P**, (Z)-1-(4-Chloro-3-hydroxyphenyl)-2-(3,4,5-trimethoxyphenyl)ethene **326850-83-3P**, (Z)-1-(4-Ethyl-3-hydroxyphenyl)-2-(3,4,5-trimethoxyphenyl)ethene
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. and use of stilbenes with vascular damaging activity)

RN 326850-81-1 CAPLUS

CN Phenol, 2-fluoro-5-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

Double bond geometry as shown.

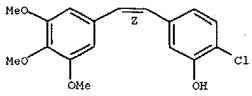


L24 ANSWER 61 OF 157 CAPLUS COPYRIGHT 2003 ACS (Continued)

RN 326850-82-2 CAPLUS

CN Phenol, 2-chloro-5-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

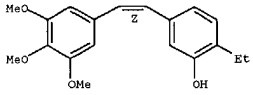
Double bond geometry as shown.



RN 326850-83-3 CAPLUS

CN Phenol, 2-ethyl-5-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



L24 ANSWER 62 OF 157 CAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 2001:125583 CAPLUS

DOCUMENT NUMBER: 134:348034

TITLE: Evaluation of combretastatin A-4 prodrug in a non-Hodgkin's lymphoma xenograft model: preclinical efficacy

AUTHOR(S): Nabha, Sanaa M.; Mohammad, Ramzi M.; Wall, Nathan R.; Dutcher, Julie A.; Salkini, Bashar M.; Pettit, George R.; Al-Katib, Ayad M.

CORPORATE SOURCE: Division of Hematology and Oncology, Department of Internal Medicine, School of Medicine, Wayne State University, Detroit, MI, 48201, USA

SOURCE: Anti-Cancer Drugs (2001), 12(1), 57-63
CODEN: ANTDEV; ISSN: 0959-4973

PUBLISHER: Lippincott Williams & Wilkins

DOCUMENT TYPE: Journal

LANGUAGE: English

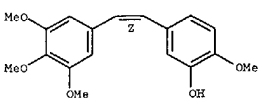
AB Combretastatin A-4 prodrug (CA4P) is a new antitubulin agent currently in phase I/II clin. trials against solid tumors. We have previously reported on the in vitro activity of CA4P against a panel of malignant human B-lymphoid cell lines. In this study, we investigated the antitumor and the antiangiogenic activity of CA4P in our diffuse large cell lymphoma WSU-DLCL2-SCID mouse model. WSU-DLCL2 cells (107) were injected s.c. into 5-wk-old female ICR-SCID mice. Tumor-bearing mice were treated at the CA4P max. tolerated dose (MTD) of 800 mg/kg in different dose/schedules. CA4P showed significant antitumor activity against this lymphoma model. Best results were seen when MTD was given in two and four divided doses (400 and 200 mg/kg, resp.). CA4P given in four divided doses (4.times.200 mg/kg) showed a log1D kill of 1.01, T/C of 11.7% and T-C of 12 days. Immunohistochem. staining using anti-CD31 antibody after 6, 24, 48 and 120 h treatment revealed a significant decrease in the no. of tumor blood vessels after 24 h (about 80%). Only the periphery of treated tumors revealed the presence of blood vessels. Morphol. examn. of the tumors after tetrachrome staining showed a necrotic center in tumors of CA4P-treated animals. New blood vessel formation was noted to emerge in tumor tissues as early as 48 h following a single dose of CA4P. The G2/M arrest obsd. in vitro was not detected in vivo indicating predominance of the antiangiogenic effects with regard to antitumor efficacy in vivo. We conclude that CA4P has antiangiogenic activity in this lymphoma model and the use of this agent should be explored clin. in the treatment of non-Hodgkin's lymphoma.

IT **117048-59-6**, Combretastatin A-4
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(evaluation of combretastatin A-4 prodrug in a non-Hodgkin's lymphoma xenograft model)

RN 117048-59-6 CAPLUS

CN Phenol, 2-methoxy-5-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

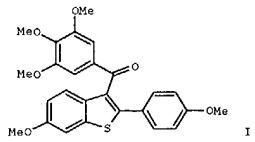
Double bond geometry as shown.



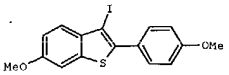
L24 ANSWER 62 OF 157 CAPLUS COPYRIGHT 2003 ACS (Continued)

REFERENCE COUNT: 23 THERE ARE 23 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L24 ANSWER 63 OF 157 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2001:85126 CAPLUS
DOCUMENT NUMBER: 134:295702
TITLE: A novel palladium-mediated coupling approach to 2,3-disubstituted benzo[b]thiophenes and its application to the synthesis of tubulin binding agents
AUTHOR(S): Flynn, Bernard L.; Verdier-Pinard, Pascal; Hamel, Ernest
CORPORATE SOURCE: Department of Chemistry The Faculties, Australian National University, Canberra, 0200, Australia
SOURCE: Organic Letters (2001), 3(5), 651-654
CODEN: ORLEF7; ISSN: 1523-7060
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 134:295702
GI



I

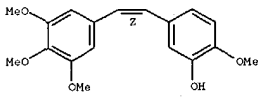


II

AB Flexible, convergent access to 2,3-disubstituted benzo[b]thiophenes, e.g. I, has been developed. The most concise approach involves sequential coupling of o-bromoiodobenzenes with benzylmercaptan and zinc acetylides to give benzyl o-ethynylphenyl sulfides which react with iodine to give 3-iodobenzo[b]thiophenes, e.g. II, in a 5-endo-dig iodocyclization. These iodides can be further elaborated using palladium-mediated coupling and/or metalation techniques. This method has been applied to the synthesis of some novel tubulin binding agents. Several products were tested for their effects on tubulin polymn., colchicine binding, and cytotoxicity in human Burkitt lymphoma.
IT **117048-59-6**, Combretastatin A4
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(prepn. of disubstituted benzothiophenes via palladium-mediated coupling reactions and their tubulin polymn./colchicine binding inhibiting-antitumor activities)
RN 117048-59-6 CAPLUS
CN Phenol, 2-methoxy-5-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA

L24 ANSWER 63 OF 157 CAPLUS COPYRIGHT 2003 ACS (Continued)
INDEX NAME)

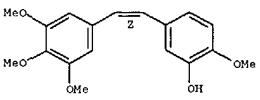
Double bond geometry as shown.



REFERENCE COUNT: 40 THERE ARE 40 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L24 ANSWER 64 OF 157 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2001:35285 CAPLUS
DOCUMENT NUMBER: 135:70797
TITLE: Combretastatin A-4 and doxorubicin combination treatment is effective in a preclinical model of human medullary thyroid carcinoma
AUTHOR(S): Nelkin, Barry D.; Ball, Douglas W.
CORPORATE SOURCE: Department of Oncology, Johns Hopkins University School of Medicine, Baltimore, MD, 21231, USA
SOURCE: Oncology Reports (2001), 8(1), 157-160
CODEN: OCRPEW; ISSN: 1021-335X
PUBLISHER: Oncology Reports
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Medullary thyroid carcinoma (MTC), both in patients and in preclin. models, is resistant to chemotherapy. In this study, we show that the anti-neovascular agent combretastatin A-4 phosphate prodrug (CA4P) in combination with doxorubicin was effective in curtailing tumor growth in a preclin. model of human MTC. This combination of combretastatin and doxorubicin extended the doubling time of established MTC tumors in nude mice to 29 days, compared to 12 days in untreated controls. This suggests that a combination of combretastatin and a cytotoxic chemotherapeutic agent may be an effective treatment for MTC.
IT **117048-59-6**, Combretastatin A-4
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(combretastatin A-4 and doxorubicin combination treatment is effective in a preclin. model of human medullary thyroid carcinoma)
RN 117048-59-6 CAPLUS
CN Phenol, 2-methoxy-5-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

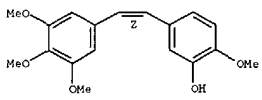
Double bond geometry as shown.



REFERENCE COUNT: 17 THERE ARE 17 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L24 ANSWER 65 OF 157 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2000:844934 CAPLUS
DOCUMENT NUMBER: 134:86019
TITLE: Design, synthesis and cytotoxic activities of naphthyl analogs of combretastatin A-4
AUTHOR(S): Maya, Ana B. S.; Del Rey, Benedicto; De Clairac, Rafael Pelaez Lamamie; Caballero, Esther; Barasoain, Isabel; Andreu, Jose Manuel; Medarde, Manuel
CORPORATE SOURCE: Laboratorio de Quimica Organica y Farmaceutica, Facultad de Farmacia, Universidad de Salamanca, Salamanca, 37007, Spain
SOURCE: Bioorganic & Medicinal Chemistry Letters (2000), 10(22), 2549-2551
CODEN: BMCLE8; ISSN: 0960-894X
PUBLISHER: Elsevier Science Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 134:86019
AB The 3,4,5-trimethoxyphenyl and 3-hydroxy-4-methoxyphenyl rings of combretastatin A-4 are deemed optimal for its activity as antimitotic agent. The replacement of either one by a naphthalene ring results in compds. with a potency comparable to that of the parent compd. These results show that the naphthalene ring is a good surrogate for the 3,4,5-trimethoxyphenyl or the 3-hydroxy-4-methoxyphenyl rings of combretastatin A-4 and that neither of them is essential for the antitumor activity.
IT **117048-59-6**, Combretastatin A-4
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(prepn. of naphthyl analogs of combretastatin A-4 as antitumor agents)
RN 117048-59-6 CAPLUS
CN Phenol, 2-methoxy-5-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



REFERENCE COUNT: 9 THERE ARE 9 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

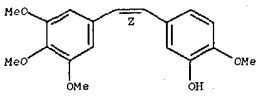
L24 ANSWER 66 OF 157 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2000:774929 CAPLUS
DOCUMENT NUMBER: 134:125660
TITLE: The Interaction of the B-ring of Colchicine with .alpha.-Tubulin: A Novel Footprinting Approach
AUTHOR(S): Chaudhuri, Asish R.; Seetharamalu, P.; Schwarz, Patricia M.; Hausheer, F. H.; Ludueа, Richard F.
CORPORATE SOURCE: Department of Biochemistry, University of Texas Health Science Center at San Antonio, TX, 78229, USA
SOURCE: Journal of Molecular Biology (2000), 303(5), 679-692
CODEN: JMOBAK; ISSN: 0022-2836
PUBLISHER: Academic Press
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Tubulin, the major structural component of the microtubules, participates actively in mitotic spindle formation and chromosomal organization during cell division. Tubulin is the major target for a variety of anti-mitotic drugs. Some of the drugs, such as Vinca alkaloids and taxol, are routinely used for cancer chemotherapy. It is unfortunate that the authors knowledge of the binding sites on tubulin of these drugs is limited because of lack of a useful and appropriate tool. The photoaffinity labeling approach is the major technique available at present to detect the binding sites of drugs on tubulin. This method, however, has several limitations. First, only part of the binding site can be identified, namely, the residues which react with the photoaffinity label. Second, there are regions of tubulin which are not at the binding site but are affected by the binding of the drug; these regions can not be detected by the photoaffinity labeling approach. The third, and perhaps most serious, limitation is that the traditional approach can detect areas which have nothing to do with the binding of the ligand but which are within a certain distance of the binding site, that distance being less than the length of the photoreactive moiety attached to the ligand. There has been a great deal of controversy on the localization of the binding site of colchicine on tubulin, with some reports suggesting that the binding site is on .alpha. and some supporting a binding site on .beta.. Colchicine also has significant effects on tubulin conformation, but the regions which are affected have not been identified. The authors have attempted here to address these questions by a novel "footprinting" method by which the drug-binding sites and as well as the domain of tubulin affected by drug-induced conformational changes could be detd. Here, the authors report for the first time that the interaction of the B-ring of colchicine with the .alpha.-subunit affects a domain of tubulin which appears to be far from its binding site. This domain includes the cysteine residues at positions 295, 305, 315 and 316 on .alpha.-tubulin; these residues are located well away from the .alpha./.beta. interface where colchicine appears to bind. This is correlated with the stabilizing effect of colchicine on the tubulin mol. Furthermore, the authors also found that the B-ring of colchicine plays a major role in the stability of tubulin while the A and the C-rings have little effect on it. Our results therefore, support a model whereby colchicine binds at the .alpha./.beta. interface of tubulin with the B-ring on the .alpha.-subunit and the A and the C-rings on the .beta.-subunit. (c) 2000 Academic Press.

IT **117048-59-6**, Combretastatin A-4
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(interaction of B-ring of colchicine with .alpha.-tubulin using novel footprinting approach to detn. drug binding)

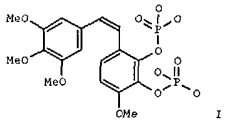
L24 ANSWER 66 OF 157 CAPLUS COPYRIGHT 2003 ACS (Continued)
RN 117048-59-6 CAPLUS
CN Phenol, 2-methoxy-5-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



REFERENCE COUNT: 48 THERE ARE 48 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L24 ANSWER 67 OF 157 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2000:757705 CAPLUS
DOCUMENT NUMBER: 134:51116
TITLE: Antineoplastic agents 429. Syntheses of the combretastatin A-1 and combretastatin B-1 prodrugs
AUTHOR(S): Pettit, George R.; Lippert, John W., III
CORPORATE SOURCE: Cancer Research Institute and Department of Chemistry and Biochemistry, Arizona State University, Tempe, AZ, 85287-2404, USA
SOURCE: Anti-Cancer Drug Design (2000), 15(3), 203-216
CODEN: ACDDEA; ISSN: 0266-9536
PUBLISHER: Oxford University Press
DOCUMENT TYPE: Journal
LANGUAGE: English
GI



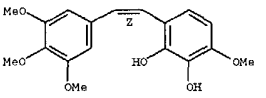
I

AB The original synthesis of combretastatin A-1 was modified to allow an efficient scale-up procedure for obtaining this antineoplastic stilbene. Subsequent conversion to a useful prodrug was accomplished by diphosphorylation, with in situ formation of dibenzylchlorophosphite, followed by cleavage of the benzyl ester protecting groups with trimethyliodosilane. The phosphoric acid intermediate was treated with sodium methoxide to complete a practical route to the sodium phosphate prodrug (I). Selective hydrogenation of phosphate deriv. and treatment of the product with sodium methoxide led to combretastatin B-1 prodrug. The phosphoric acid precursor of prodrug I was employed in a parallel series of reactions to produce a selection of metal and ammonium cation prodrug candidates. Each of the phosphate salts was evaluated from the perspective of relative soly. behavior and cancer cell growth inhibition. The sodium phosphate prodrug I was selected for detailed antineoplastic studies.

IT **109971-63-3P**, Combretastatin A-1
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(prepn. of antineoplastic agents, combretastatin A-1 and combretastatin B-1 prodrugs)
RN 109971-63-3 CAPLUS
CN 1,2-Benzenediol, 3-methoxy-6-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

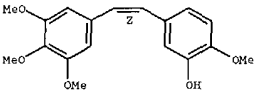
Double bond geometry as shown.

L24 ANSWER 67 OF 157 CAPLUS COPYRIGHT 2003 ACS (Continued)



IT **117048-59-6**, Combretastatin a4
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(prepn. of antineoplastic agents, combretastatin A-1 and combretastatin B-1 prodrugs)
RN 117048-59-6 CAPLUS
CN Phenol, 2-methoxy-5-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



IT **109984-84-1P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(prepn. of antineoplastic agents, combretastatin A-1 and combretastatin B-1 prodrugs)
RN 109984-84-1 CAPLUS
CN 1,2-Benzenediol, 3-methoxy-6-[(1E)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

Double bond geometry as shown.

REFERENCE COUNT: 94 THERE ARE 94 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L24 ANSWER 68 OF 157 CAPLUS COPYRIGHT 2003 ACS

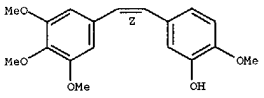
ACCESSION NUMBER: 2000:754871 CAPLUS
DOCUMENT NUMBER: 134:260980
TITLE: Combretastatins: novel vascular targeting drugs for improving anticancer therapy. Combretastatins and conventional therapy
AUTHOR(S): Horsman, M. R.; Murata, R.; Breidahl, T.; Nielsen, F. U.; Maxwell, R. J.; Stodkilde-Jorgensen, H.; Overgaard, J.
CORPORATE SOURCE: Danish Cancer Society, Department of Experimental Clinical Oncology, Aarhus University Hospital and MR-Centre, Aarthus, Den.
SOURCE: Advances in Experimental Medicine and Biology (2000), 476(Angiogenesis: From the Molecular to Integrative Pharmacology), 311-323
CODEN: AEMBAP; ISSN: 0065-2598
PUBLISHER: Kluwer Academic/Plenum Publishers
DOCUMENT TYPE: Journal
LANGUAGE: English

AB This study investigated the potential of combretastatin A-4 disodium phosphate (CA4DP) to induce vascular effects in a C3H mouse mammary carcinoma and studied whether the antitumor response could be improved by combining the drug with conventional anticancer therapies. CA4DP (250 mg/kg) decreased tumor perfusion within 30 min after injection and maintained this effect for several hours, although there was a return to normal by 24 h. Similar changes were seen in the bioenergetic and oxygenation status of the tumors. The drug also increased tumor necrosis and had a small inhibitory effect on tumor growth. It was also able to enhance the tumor response to radiation and hyperthermia, when given at the same time or 30 min after radiation and hyperthermia, resp. Giving the drug 1 h after cisplatin injection resulted only in a tumor response that was no greater than additive. These results confirm the antivascular effects of CA4DP and demonstrate its potential to enhance the antitumor activity of conventional therapy.

IT **117048-59-6**, Combretastatin A4
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(antitumor activity of combretastatin A4 and its interaction with radiotherapy and hyperthermia)

RN 117048-59-6 CAPLUS
CN Phenol, 2-methoxy-5-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



REFERENCE COUNT: 33 THERE ARE 33 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L24 ANSWER 68 OF 157 CAPLUS COPYRIGHT 2003 ACS (Continued)

L24 ANSWER 69 OF 157 CAPLUS COPYRIGHT 2003 ACS

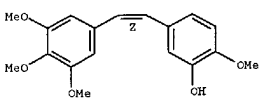
ACCESSION NUMBER: 2000:726998 CAPLUS
DOCUMENT NUMBER: 134:29214
TITLE: Natural organic compounds that affect to microtubule functions: syntheses and structure-activity relationships of Combretastatins, Curacin A and their analogs as the Colchicine-site ligands on tubulin
AUTHOR(S): Iwasaki, Shigeo; Shirai, Ryuichi
CORPORATE SOURCE: Research Center for Biological Function, Kitasato Institute, Tokyo, 108-8642, Japan
SOURCE: Yakugaku Zasshi (2000), 120(10), 875-890
CODEN: YKKZAJ; ISSN: 0031-6903
PUBLISHER: Pharmaceutical Society of Japan
DOCUMENT TYPE: Journal; General Review
LANGUAGE: Japanese

AB A review with 38 refs. Microtubules (MT) are cylindrical polymers of the protein tubulin (TN) .alpha.,.beta.-heterodimer, and are known to be the main component of spindles in mitotic app. of eucaryotic cells. MT are also involved in many other basic and essential cell functions. There are a no. of natural and synthetic compds. that interfere with MT function to cause the mitotic arrest of eucaryotic cells. Such antimitotic agents show a broad biol. activity, and can be used for medicinal and agrochem. purposes. On the other hand, they are important also as the biochem. tools for understanding the dynamics of MT network. Most of such antimitotic agents, with a few exceptions, bind to .beta.-TN. Among them, colchicine (CLC), vinblastine and taxol have played major roles in practical uses as well as in biochem. studies of MT functions. They all bind to .beta.-TN but their binding sites are different. The authors have worked on a variety of antimitotic agents that bind to either of colchicine-site, vinblastine-site and taxol-site, in discovery, structures, biol. actions and/or interactions with TN. In this paper, the results of the authors' studies on CLC-site ligands were summarized; (1) synthetic analogs of combretastatin A-4 (CBS A-4), isolated as a cytotoxic compd. produced by a species of South African tree Combretum caffrum, (2) curacin A (CU-A), a cytotoxic metabolite of a marine cyanobacteria Lyngbya majuscula, and its related compds. Interactions of these compds. with TN were studied and structure-activity relationships of these two classes of compds. were discussed.

IT **117048-59-6DP**, Combretastatin A-4, analogs
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(natural org. compds. having affect on microtubule functions and synthesis and structure-activity relationships of combretastatins, curacin A and analogs as colchicine-site ligands on tubulin)

RN 117048-59-6 CAPLUS
CN Phenol, 2-methoxy-5-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

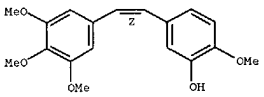
Double bond geometry as shown.



L24 ANSWER 69 OF 157 CAPLUS COPYRIGHT 2003 ACS (Continued)

L24 ANSWER 70 OF 157 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2000:658688 CAPLUS
DOCUMENT NUMBER: 134:52722
TITLE: Synthesis and biological evaluation of aryl azide derivatives of combretastatin A-4 as molecular probes for tubulin
AUTHOR(S): Pinney, K. G.; Mejia, M. P.; Villalobos, V. M.; Rosenquist, B. E.; Pettit, G. R.; Verdier-Pinard, P.; Hamel, E.
CORPORATE SOURCE: Department of Chemistry and Biochemistry, Baylor University, Waco, TX, 76798-7348, USA
SOURCE: Bioorganic & Medicinal Chemistry (2000), 8(10), 2417-2425
CODEN: BMECEP; ISSN: 0968-0896
PUBLISHER: Elsevier Science Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 134:52722
AB Two new aryl azides, (Z)-1-(3'-azido-4'-methoxyphenyl)-2-(3'',4'',5''-trimethoxyphenyl)ethene [I] and (Z)-1-(4'-azido-3'-methoxyphenyl)-2-(3'',4'',5''-trimethoxyphenyl)ethene [II], modeled after the potent antitumor, antimitotic agent combretastatin A-4 (CA-4), have been prepd. by chem. synthesis as potentially useful photoaffinity labeling reagents for the colchicine site on .beta.-tubulin. Aryl azide I, in which the 3'-hydroxyl group of CA-4 is replaced by an azido moiety, demonstrates excellent in vitro cytotoxicity against human cancer cell lines (NCI 60 cell line panel, av. GI50=4.07.times.10-8 M) and potent inhibition of tubulin polymn. (IC50=1.4.+-.0.1 .mu.M). The 4'-azido analog II has lower activity (NCI 60 cell line panel, av. GI50=2.28.times.10-6 M, and IC50=5.2 .+-.0.2 .mu.M for inhibition of tubulin polymn.), suggesting the importance of the 4'-methoxy moiety for interaction with the colchicine binding site on tubulin. These CA-4 aryl azide analogs also inhibit binding of colchicine to tubulin, as does the parent CA-4, and therefore these compds. are excellent candidates for photoaffinity labeling studies.
IT **117048-59-6**, Combretastatin A4 **117048-59-6D**, Combretastatin A-4, analogs
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(synthesis and biol. evaluation of aryl azide derivs. of combretastatin A-4 as mol. probes for tubulin)
RN 117048-59-6 CAPLUS
CN Phenol, 2-methoxy-5-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

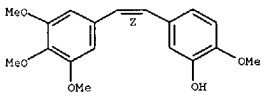
Double bond geometry as shown.



RN 117048-59-6 CAPLUS

L24 ANSWER 70 OF 157 CAPLUS COPYRIGHT 2003 ACS (Continued)
CN Phenol, 2-methoxy-5-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

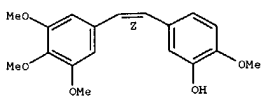
Double bond geometry as shown.



REFERENCE COUNT: 52 THERE ARE 52 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L24 ANSWER 71 OF 157 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2000:656267 CAPLUS
DOCUMENT NUMBER: 133:246908
TITLE: Antiangiogenic treatment of human non-small cell lung cancer (NSCLC) in a murine xenotransplant model
AUTHOR(S): Bohle, A. S.; Dohrmann, P.; Kalthoff, H.; Henne-Bruns, D.
CORPORATE SOURCE: Klinik fur Allgemeine Chirurgie und Thoraxchirurgie, Arbeitsgruppe Molekulare Onkologie, Christian-Albrechts-Universitat zu Kiel, Kiel, 24105, Germany
SOURCE: Chirurgisches Forum fuer Experimentelle und Klinische Forschung (2000) 403-407
CODEN: CFEKA7; ISSN: 0303-6227
PUBLISHER: Springer-Verlag
DOCUMENT TYPE: Journal
LANGUAGE: German
AB The aim of this study was to evaluate the biol. effect of the antiangiogenic agent CA4PD on human non-small cell lung cancer (NSCLC) in a murine xenotransplant model. Human NSCLC were treated by systemic administration of the antiangiogenic agent CA4PD in a heterotopic, s.c. tumor model and a lethal, ortho-topic human lung cancer tumor model. Systemic administration of the agent CA4PD resulted, in s.c. induced tumors, in a redn. of tumor growth. After ortho-topic tumor induction in the lung, survival was prolonged by 29% and 35%, resp. Systemic antiangiogenic treatment of human NSCLC in the murine xenotransplant model is effective in reducing tumor proliferation and prolonging animal survival.
IT **117048-59-6**, Combretastatin-A4
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(prodrug; antiangiogenic treatment of human non-small cell lung cancer in a xenotransplant model with CA4PD)
RN 117048-59-6 CAPLUS
CN Phenol, 2-methoxy-5-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

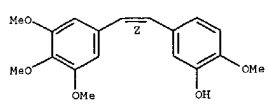
Double bond geometry as shown.



REFERENCE COUNT: 7 THERE ARE 7 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L24 ANSWER 72 OF 157 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2000:647330 CAPLUS
DOCUMENT NUMBER: 134:141436
TITLE: Combretastatin A-4 prodrug: A potent inhibitor of malignant hemangioendothelioma cell proliferation
AUTHOR(S): Bohle, A. S.; Leuschner, I.; Kalthoff, H.; Henne-Bruns, D.
CORPORATE SOURCE: Department of General Surgery and Thoracic Surgery, Christian-Albrechts-University, Kiel, 24105, Germany
SOURCE: International Journal of Cancer (2000), 87(6), 838-843
CODEN: IJCNAW; ISSN: 0020-7136
PUBLISHER: Wiley-Liss, Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Anti-vascular treatment by targeting proliferating endothelial cells has become a promising option in anti-neoplastic therapy. Combretastatin A-4 prodrug (CA-4PD) has been identified as a selective inhibitor of endothelial cell proliferation, acting by the interruption of microtubule assembly. In this study, the effect of CA-4PD on proliferating endothelial cells derived from a primary tumor of the vascular endothelium was investigated in vitro and in vivo. In vitro, CA-4PD was an effective inhibitor of endothelial cell proliferation in a time- and dose-dependent manner, displaying a certain selectivity toward endothelial cells in comparison to proliferating fibroblasts. Anal. of DNA profiles by FACS revealed an increasing proportion of cells arrested in the G2 cell-cycle phase with correlation to the duration of drug exposure. A decrease in cell viability correlated with duration of drug exposure, whereas FACS anal., DNA fragmentation assay, and DNA gel electrophoresis failed to demonstrate that DNA fragmentation was indicative of apoptosis up to 48 h of continued drug exposure. In vivo, CA-4PD induced excessive regressive alterations in exptl. allotransplanted hemangioendotheliomas within 24 h after singular i.p. injection of 100 mg CA-4PD/kg body wt. This represented less than one-tenth of the max. tolerated dose. In conclusion, our findings characterize CA-4PD as a potent inhibitor of malignant endothelial cell proliferation in vitro, effecting arrest of proliferating cells in the G2 cell-cycle phase with subsequent cell death on a pathway different from apoptosis. In vivo, CA-4PD induces extensive intratumoral cell loss within 24 h following systemic administration, suggesting a synergistic effect of direct cell killing and the induction of vascular shutdown.
IT **117048-59-6**, Combretastatin A-4
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(combretastatin A-4 prodrug, a potent inhibitor of malignant hemangioendothelioma cell proliferation)
RN 117048-59-6 CAPLUS
CN Phenol, 2-methoxy-5-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



L24 ANSWER 72 OF 157 CAPLUS COPYRIGHT 2003 ACS (Continued)
REFERENCE COUNT: 21 THERE ARE 21 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L24 ANSWER 73 OF 157 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2000:592560 CAPLUS
DOCUMENT NUMBER: 133:198575
TITLE: Compositions and methods for use in targeting vascular destruction
INVENTOR(S): Pero, Ronald W.; Sherris, David
PATENT ASSIGNEE(S): Oxigene, Inc., USA
SOURCE: PCT Int. Appl., 36 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

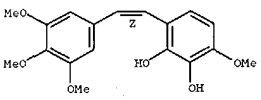
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000048606	A1	20000824	WO 2000-US3996	20000216
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
CA 2358925	AA	20000824	CA 2000-2358925	20000216
EP 1152764	A1	20011114	EP 2000-914606	20000216
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
JP 2002537262	T2	20021105	JP 2000-599398	20000216
US 6538038	B1	20030325	US 2000-505402	20000216
US 2003109500	A1	20030612	US 2002-218833	20020814

PRIORITY APPLN. INFO.: US 1999-120478P P 19990218
US 2000-505402 A1 20000216
WO 2000-US3996 W 20000216

OTHER SOURCE(S): MARPAT 133:198575
AB Treatment of warm-blooded animals having a tumor or non-malignant hypervascularization, by administering a sufficient amt. of a cytotoxic agent formulated into a phosphate prodrug form having substrate specificity for microvessel phosphatases, so that microvessels are destroyed preferentially over other normal tissues, because the less cytotoxic prodrug form is converted to the highly cytotoxic dephosphorylated form.
IT **109971-63-3**
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(prodrugs for use in targeting vascular destruction)
RN 109971-63-3 CAPLUS
CN 1,2-Benzenediol, 3-methoxy-6-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

Double bond geometry as shown.

L24 ANSWER 73 OF 157 CAPLUS COPYRIGHT 2003 ACS (Continued)



REFERENCE COUNT: 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

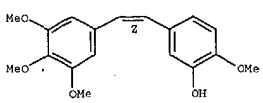
L24 ANSWER 74 OF 157 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2000:592548 CAPLUS
DOCUMENT NUMBER: 133:177486
TITLE: Preparation of substituted stilbene compounds with vascular damaging activity
INVENTOR(S): Davis, Peter David
PATENT ASSIGNEE(S): Angiogene Pharmaceuticals Ltd., UK
SOURCE: PCT Int. Appl., 31 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000048590	A1	20000824	WO 2000-GB503	20000215
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
EP 1154767	A1	20011121	EP 2000-903824	20000215
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
JP 2002537250	T2	20021105	JP 2000-599382	20000215

PRIORITY APPLN. INFO.: GB 1999-3403 A 19990216
WO 2000-GB503 W 20000215

OTHER SOURCE(S): MARPAT 133:177486
AB A vascular damaging agent AXB (A = substituted cis-stilbene; X = linker bond, atom, or group; B = moiety derived from an inhibitor of the formation or action of NO in mammalian systems), is claimed. Thus, (Z)-1-[3-(N-.alpha.-tert-butoxycarbonyl-N-.omega.-nitroarginyloxy)-4-methoxyphenyl]-2-(3,4,5-trimethoxyphenyl)ethene was stirred with CF3CO2H in CH2Cl2 to give (Z)-1-(4-methoxy-3-NG-nitroarginyloxyphenyl)-2-(3,4,5-trimethoxyphenyl)ethene. The latter at 50 mg/kg i.p. in mice bearing CaNT or SaS tumors gave 95% redn. in vascular vol. and 91-100% tumor necrosis.
IT **117048-59-6**
RL: RCT (Reactant); RACT (Reactant or reagent)
(prepn. of substituted stilbene compds. with vascular damaging activity)
RN 117048-59-6 CAPLUS
CN Phenol, 2-methoxy-5-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

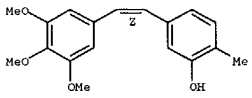
Double bond geometry as shown.



IT **288585-59-1P**

L24 ANSWER 74 OF 157 CAPLUS COPYRIGHT 2003 ACS (Continued)
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(prepn. of substituted stilbene compds. with vascular damaging activity)
RN 288585-59-1 CAPLUS
CN Phenol, 2-methyl-5-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

Double bond geometry as shown.

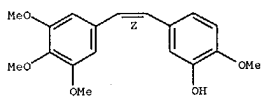


REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L24 ANSWER 75 OF 157 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2000:503373 CAPLUS
DOCUMENT NUMBER: 133:202672
TITLE: Effects of combretastatin A-4 prodrug against a panel of malignant human B-lymphoid cell lines
AUTHOR(S): Nabha, Sanaa M.; Wall, Nathan R.; Mohammad, Ramzi M.; Pettit, George R.; Al-Katib, Ayad M.
CORPORATE SOURCE: Division of Hematology and Oncology, Karmanos Cancer Institute, School of Medicine, Wayne State University, Detroit, MI, 48201, USA
SOURCE: Anti-Cancer Drugs (2000), 11(5), 385-392
CODEN: ANTDEV; ISSN: 0959-4973
PUBLISHER: Lippincott Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Combretastatin A-4 (CA-4) is one of a family of compds. isolated from the South African willow tree Combretum caffrum. CA-4 was active against murine melanoma and a variety of other human solid tumors. For the first time, we report the effect of CA-4 against a panel of malignant human B-lymphoid cell lines [early pre-B acute lymphoblastic leukemia (Reh), diffuse large cell lymphoma (WSU-DLCL2), chronic lymphocytic leukemia (WSU-CLL) and Waldenstrom's macroglobulinemia (WSU-WM)]. Our results indicate, using the prodrug form of CA-4, a concn.-dependent growth inhibition in all tested cell lines, although WSU-DLCL2 was more sensitive. Exposure to 4 nM CA-4 for 96 h induced 77% growth inhibition in Reh, 86% in WSU-CLL and 92% in WSU-WM. When used against the WSU-DLCL2 cell line, this same concn. of CA-4 was completely toxic. Morphol. examn. showed CA-4 induced the formation of giant, multinucleated cells, a phenomenon commonly found in mitotic catastrophe. Only minimal nos. of cells showing characteristics of apoptosis were detected. In WSU-DLCL2 cells, CA-4 (3 nM) induced the highest apoptosis (5%) after 48 h, while the percentage of dead cells was approx. 47%. Exposure of Reh, WSU-CLL, WSU-WM and WSU-DLCL2 cells for 24 h to 5 nM CA-4 induced 19, 28, 57 and 75% G2/M arrest, as detd. by flow cytometry, resp. Based on these preliminary studies, we believe that mitotic catastrophe is the predominant mechanism by which CA-4 induces cell death rather than apoptosis. Further studies to elucidate the mechanisms of CA-4 activity in vitro and in vivo are currently under investigation in our lab.
IT **117048-59-6**, Combretastatin A-4
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(effects of combretastatin A-4 prodrug against a panel of malignant human B-lymphoid cell lines)
RN 117048-59-6 CAPLUS
CN Phenol, 2-methoxy-5-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

Double bond geometry as shown.

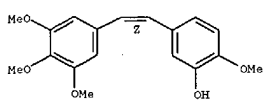
L24 ANSWER 75 OF 157 CAPLUS COPYRIGHT 2003 ACS (Continued)



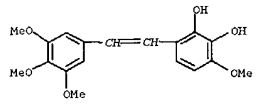
REFERENCE COUNT: 27 THERE ARE 27 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L24 ANSWER 76 OF 157 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2000:454837 CAPLUS
DOCUMENT NUMBER: 133:234061
TITLE: Comparative molecular field analysis of colchicine inhibition and tubulin polymerization for combretastatins binding to the colchicine binding site on .beta.-tubulin
AUTHOR(S): Brown, M. L.; Rieger, J. M.; Macdonald, T. L.
CORPORATE SOURCE: Chemistry Department, University of Virginia, Charlottesville, VA, 22904-4319, USA
SOURCE: Bioorganic & Medicinal Chemistry (2000), 8(6), 1433-1441
CODEN: BMECEP; ISSN: 0968-0896
PUBLISHER: Elsevier Science Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB A mol. modeling study using Comparative Mol. Field Anal. (CoMFA) was undertaken to develop a predictive model for combretastatin binding to the colchicine binding site of tubulin. Furthermore, we examd. the potential contribution of lipophilicity (log P) and mol. dipole moment and were unable to correlate these properties to the obsd. biol. data. In this study we first confirmed that tubulin polymn. inhibition (IC50) correlated (R2=0.92) with [3H]colchicine displacement. Although these data correlated quite well, we developed two independent models for each set of data to quantify structural features that may contribute to each biol. property independently. To develop our predictive model we first examd. a series of mol. alignments for the training set and ultimately found that overlaying the resp. trimethoxyphenyl rings (A ring) of the analogs generated the best correlated model. The CoMFA yielded a cross-validated R2=0.41 (optimum no. of components equal to 5) for the tubulin polymn. model and an R2=0.38 (optimum no. of components equal to 5) for [3H]colchicine inhibition. Final non-cross-validation generated models for tubulin polymn. (R2 of 0.93) and colchicine inhibition (R2 of 0.91). These models were validated by predicting both biol. properties for compds. not used in the training set. These models accurately predicted the IC50 for tubulin polymn. with an R2 of 0.88 (n=6) and those of [3H]colchicine displacement with an R2 of 0.80 (n=7). This study represents the first predictive model for the colchicine binding site over a wide range of combretastatin analogs.
IT **117048-59-6**, Combretastatin A4 **293301-40-3**
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study); PROC (Process)
(comparative mol. field anal. of colchicine inhibition and tubulin polymn. for combretastatins binding to the colchicine binding site on .beta.-tubulin)
RN 117048-59-6 CAPLUS
CN Phenol, 2-methoxy-5-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

Double bond geometry as shown.

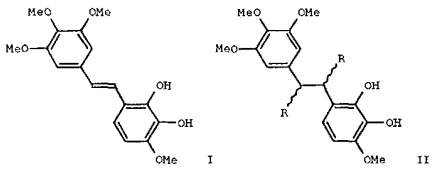


L24 ANSWER 76 OF 157 CAPLUS COPYRIGHT 2003 ACS (Continued)
RN 293301-40-3 CAPLUS
CN 1,2-Benzenediol, 3-methoxy-6-[2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 26 THERE ARE 26 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L24 ANSWER 77 OF 157 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2000:443011 CAPLUS
DOCUMENT NUMBER: 133:207722
TITLE: Antineoplastic Agents 440. Asymmetric Synthesis and Evaluation of the Combretastatin A-1 SAR Probes (1S,2S)- and (1R,2R)-1,2-Dihydroxy-1-(2',3'-dihydroxy-4'-methoxyphenyl)-2-(3'',4'',5''-trimethoxyphenyl)-ethane
AUTHOR(S): Pettit, George R.; Lippert, John W., III; Herald, Delbert L.; Hamel, Ernest; Pettit, Robin K.
CORPORATE SOURCE: Cancer Research Institute and Department of Chemistry, Arizona State University, Tempe, AZ, 85287-2404, USA
SOURCE: Journal of Natural Products (2000), 63(7), 969-974
CODEN: JNPRDF; ISSN: 0163-3864
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
GI

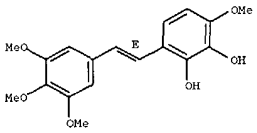


AB The synthetic (E)-isomer (I) of natural combretastatin A-1 isolated from the African bushwillow Combretum caffrum was the focus of chiral hydroxylation (Sharpless) reactions as part of a structure-activity relationship study. The resulting (R,R)- (II; R = .alpha.-OH) (III) and (S,S,)-diols II (R = .beta.-OH) (IV) and synthetic intermediates were evaluated against a series of cancer cell lines, microorganisms, and tubulin. Chiral diols III and IV showed increased activity against the P-388 murine lymphocytic leukemia cell line with ED50 values of 3.9 and 2.9 .mu.g/mL, resp., when compared to the precursor (E)-stilbene I. In contrast, I exhibited more potent antibiotic activity than the chiral diols, III and IV. Both diols, III and IV, displayed less cancer cell growth inhibition and less antibiotic activity than did natural combretastatin A-1 (P-388 ED50 0.25 .mu.g/mL).

IT ***109984-84-1 117048-62-1***
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(antimicrobial activity of, in structure activity relationship study of the combretastatin A1 SAR probes)

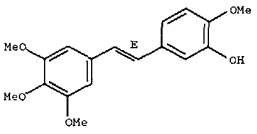
RN 109984-84-1 CAPLUS
CN 1,2-Benzenediol, 3-methoxy-6-[(1E)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

L24 ANSWER 77 OF 157 CAPLUS COPYRIGHT 2003 ACS (Continued)
Double bond geometry as shown.



RN 117048-62-1 CAPLUS
CN Phenol, 2-methoxy-5-[(1E)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

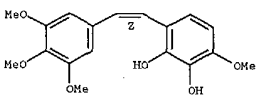
Double bond geometry as shown.



IT **109971-63-3 117048-59-6**
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(cytotoxicity, antimicrobial and tubulin polymn. inhibitory activity of, in structure activity relationship study of the combretastatin A1 SAR probes)

RN 109971-63-3 CAPLUS
CN 1,2-Benzenediol, 3-methoxy-6-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

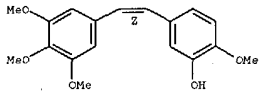
Double bond geometry as shown.



RN 117048-59-6 CAPLUS
CN Phenol, 2-methoxy-5-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

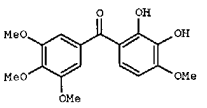
Double bond geometry as shown.

L24 ANSWER 77 OF 157 CAPLUS COPYRIGHT 2003 ACS (Continued)



REFERENCE COUNT: 50 THERE ARE 50 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L24 ANSWER 78 OF 157 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2000:425859 CAPLUS
DOCUMENT NUMBER: 133:207717
TITLE: Antineoplastic Agents. 443. Synthesis of the Cancer Cell Growth Inhibitor Hydroxyphenstatin and Its Sodium Diphosphate Prodrug
AUTHOR(S): Pettit, George R.; Grealish, Matthew P.; Herald, Delbert L.; Boyd, Michael R.; Hamel, Ernest; Pettit, Robin K.
CORPORATE SOURCE: Cancer Research Institute and Department of Chemistry and Biochemistry, Arizona State University, Tempe, AZ, 85287-2404, USA
SOURCE: Journal of Medicinal Chemistry (2000), 43(14), 2731-2737
CODEN: JMCMAR; ISSN: 0022-2623
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
GI



I

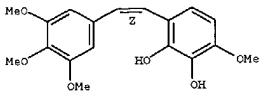
AB A structure-activity relationship (SAR) study of the South African willow tree (Combretum caffrum) antineoplastic constituent combretastatin A-4 led to the discovery of a potent cancer cell growth inhibitor designated phenstatin. This benzophenone deriv. of combretastatin A-4 showed remarkable antineoplastic activity, and the benzophenone deriv. of combretastatin A-1 was therefore synthesized. The benzophenone, designated hydroxyphenstatin (I), was synthesized by coupling of a protected bromobenzene and a benzaldehyde to give the benzhydrol with subsequent oxidn. to the ketone. Hydroxyphenstatin was converted to the sodium phosphate prodrug by a dibenzyl phosphite phosphorylation and subsequent benzyl cleavage. While hydroxyphenstatin I was a potent inhibitor of tubulin polymn. with activity comparable to that of combretastatin A-1, the phosphorylated deriv. of I was inactive.

IT **109971-63-3**, Combretastatin A-1 **117048-59-6**, Combretastatin A-4
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(synthesis of cancer cell growth inhibitor hydroxyphenstatin and sodium diphosphate prodrug)

RN 109971-63-3 CAPLUS
CN 1,2-Benzenediol, 3-methoxy-6-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

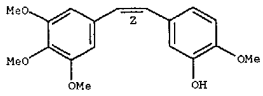
Double bond geometry as shown.

L24 ANSWER 78 OF 157 CAPLUS COPYRIGHT 2003 ACS (Continued)



RN 117048-59-6 CAPLUS
CN Phenol, 2-methoxy-5-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



REFERENCE COUNT: 32 THERE ARE 32 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

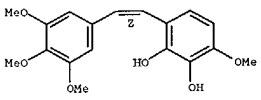
L24 ANSWER 79 OF 157 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2000:402212 CAPLUS
DOCUMENT NUMBER: 134:190683
TITLE: Bioactive compounds from Combretum erythrophyllum. [Erratum to document cited in CA132:345465]
AUTHOR(S): Schwikkard, Sianne; Zhou, Bing-Nan; Glass, Thomas E.; Sharp, Jessica L.; Mattern, Michael R.; Johnson, Randall K.; Kingston, David G. I.
CORPORATE SOURCE: Department of Chemistry, Virginia Polytechnic Institute and State University, Blacksburg, VA, 24061-0212, USA
SOURCE: Journal of Natural Products (2000), 63(7), 1046
CODEN: JNPRDF; ISSN: 0163-3864
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Compds. 1 and 2 have been previously reported from Combretum krausii by Verotta and colleagues [Pelizzoni, F.; Verotta, L. Rogers, C. B.; Colombo, R.; Pedrotti, B.; Balconi, G.; Erba, E.; D'Incalci. M. Nat. Prod. Lett. 1993, 1, 273-280], and their synthesis has also been reported [Orsini, F.; Pelizzoni, F.; Bellini, B.; Miglierini, G. Carbohydr. Res. 1997, 301, 95-109.].

IT **109971-63-3P**, Combretastatin A-1 **156085-79-9P**
RL: BAC (Biological activity or effector, except adverse); BOC (Biological occurrence); BSU (Biological study, unclassified); PRP (Properties); PUR (Purification or recovery); SPN (Synthetic preparation); BIOL (Biological study); OCCU (Occurrence); PREP (Preparation)
(isolation of bioactive compds. from Combretum erythrophyllum (Erratum))

RN 109971-63-3 CAPLUS
CN 1,2-Benzenediol, 3-methoxy-6-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

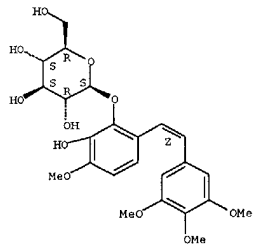
Double bond geometry as shown.



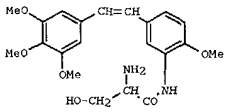
RN 156085-79-9 CAPLUS
CN .beta.-D-Glucopyranoside, 2-hydroxy-3-methoxy-6-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]phenyl (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).
Double bond geometry as shown.

L24 ANSWER 79 OF 157 CAPLUS COPYRIGHT 2003 ACS (Continued)



L24 ANSWER 80 OF 157 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2000:373651 CAPLUS
DOCUMENT NUMBER: 133:129612
TITLE: Synthesis and antitumor activities of amino acid prodrugs of amino-combretastatins
AUTHOR(S): Ohsumi, Koji; Hatanaka, Toshihiro; Nakagawa, Ryusuke; Fukuda, Yumiko; Morinaga, Yoshihiro; Suga, Yasuyo; Nihei, Yukio; Ohishi, Kazuo; Akiyama, Yukio; Tsuji, Takashi
CORPORATE SOURCE: Pharmaceutical Research Laboratories, Ajinomoto Co. Inc., Kawasaki, 210-8681, Japan
SOURCE: Anti-Cancer Drug Design (1999), 14(6), 539-548
CODEN: ACDDEA; ISSN: 0266-9536
PUBLISHER: Oxford University Press
DOCUMENT TYPE: Journal
LANGUAGE: English
GI

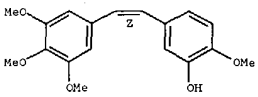


I

AB The synthesis and antitumor activity of water-sol. amino acid prodrugs of amino-combretastatins are reported. Among the synthesized compds., AC-7700 (I-HCl) showed enhanced antitumor activity and decreased toxicity in a Colon 26 murine adenocarcinoma model. I showed improved soly. and was easily formulated for in vivo administration. I was cleaved to generate the parent compd., CS-39, in the whole blood of mice as well as man, possibly by the action of amino peptidase on the erythrocyte membrane.

IT **117048-59-6**, Combretastatin A-4
RL: PRP (Properties)
(synthesis and antitumor activities of amino acid prodrugs of amino-combretastatins)
RN 117048-59-6 CAPLUS
CN Phenol, 2-methoxy-5-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



L24 ANSWER 80 OF 157 CAPLUS COPYRIGHT 2003 ACS (Continued)

REFERENCE COUNT: 18 THERE ARE 18 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

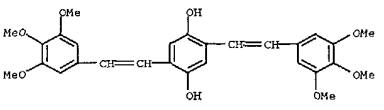
L24 ANSWER 81 OF 157 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2000:351266 CAPLUS
DOCUMENT NUMBER: 132:345122
TITLE: Sensor comprising an oligomer binding layer and method of making such sensor and arrays of such sensors
INVENTOR(S): Huyberechts, Guido; Jordens, Sven
PATENT ASSIGNEE(S): Interuniversitair Micro-Elektronica Centrum Vzw, Belg.; Universitaire Instituut Antwerpen
SOURCE: Eur. Pat. Appl., 18 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 1003033	A1	20000524	EP 1999-870236	19991116
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
EP 1003032	A1	20000524	EP 1998-870254	19981117
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				

PRIORITY APPLN. INFO.: EP 1998-870254 A 19981117
US 1999-122211P P 19990301

AB An aim of the invention is to provide a new type of sensor, capable of recognizing and/or quantifying analytes in a fluid. A further aim of the present invention is to provide such sensors with an oligomer material as a binding layer. A further aim of the present invention is to provide a novel method for the manuf. of such sensor wherein the oligomer layer is locally deposited on the sites of the sensor having a multitude of sensing sites. A biomol. recognizing an analyte is bound to the oligomer.

IT **270069-97-1DP**, alkyl derivs.
RL: ARG (Analytical reagent use); DEV (Device component use); RCT (Reactant); SPN (Synthetic preparation); ANST (Analytical study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(as oligomer; sensor comprising oligomer binding layer and method of making such sensor and arrays of such sensors)
RN 270069-97-1 CAPLUS
CN 1,4-Benzenediol, 2,5-bis[2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 7 THERE ARE 7 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

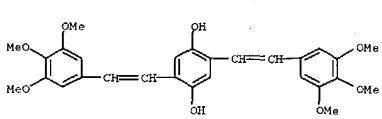
L24 ANSWER 82 OF 157 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2000:351265 CAPLUS
DOCUMENT NUMBER: 132:345121
TITLE: Sensor comprising an oligomer binding layer and method of making such sensor and arrays of such sensors
INVENTOR(S): Huyberechts, Guido; Jordens, Sven
PATENT ASSIGNEE(S): Interuniversitair Micro-Elektronica Centrum Vzw, Belg.; Universitaire Instelling Antwerpen
SOURCE: Eur. Pat. Appl., 14 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 1003032	A1	20000524	EP 1998-870254	19981117
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
EP 1003033	A1	20000524	EP 1999-870236	19991116
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
US 2002048751	A1	20020425	US 1999-441118	19991117

PRIORITY APPLN. INFO.: EP 1998-870254 A 19981117
US 1999-122211P P 19990301

AB An aim of the invention is to provide a new type of sensor, capable of recognizing and/or quantifying analytes in a fluid. A further aim of the present invention is to provide such sensors with an oligomer material as a binding layer. A further aim of the present invention is to provide a novel method for the manuf. of such sensor wherein the oligomer layer is locally deposited on the sites of the sensor having a multitude of sensing sites. A biomol. recognizing an analyte is bound to the oligomer.

IT **270069-97-1DP**, alkyl derivs.
RL: ARG (Analytical reagent use); DEV (Device component use); RCT (Reactant); SPN (Synthetic preparation); ANST (Analytical study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(as oligomer; sensor comprising oligomer binding layer and method of making such sensor and arrays of such sensors)
RN 270069-97-1 CAPLUS
CN 1,4-Benzenediol, 2,5-bis[2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 7 THERE ARE 7 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

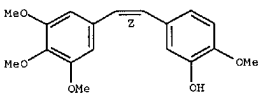
L24 ANSWER 83 OF 157 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2000:279432 CAPLUS
DOCUMENT NUMBER: 133:171912
TITLE: Combination chemotherapy with combretastatin A-4 phosphate and 5-fluorouracil in an experimental murine colon adenocarcinoma
AUTHOR(S): Grosios, K.; Loadman, P. M.; Swaine, D. J.; Pettit, G. R.; Bibby, M. C.
CORPORATE SOURCE: Clinical Oncology Unit, University of Bradford, Bradford, BD71DP, UK
SOURCE: Anticancer Research (2000), 20(1A), 229-233
CODEN: ANTRD4; ISSN: 0250-7005
PUBLISHER: International Institute of Anticancer Research
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The di-sodium phosphate pro-drug of combretastatin-A4(combA-4P) is undergoing Phase 1 clin. trial in the USA and UK. Its mechanism of action is thought to be related to tubulin-binding properties that result in rapid, tumor endothelial cell damage, neo-vascular shutdown and subsequent hemorrhagic necrosis. Drugs that work by this mechanism are unlikely to eradicate the tumor as a single agent but should potentiate std. chemotherapy. This study demonstrates that extensive necrosis occurred in a treated refractory murine colon adenocarcinoma but the damage was not accompanied by any measurable effect on tumor growth. Tumors continued to grow from the viable rim that remained. Combination chemotherapy with 5-fluorouracil (5-FU) resulted in significant ($p<0.01$) antitumor effects. Measurement of 5-FU concns. suggested that this was true synergism and not simply a pharmacokinetic interaction due to the vascular mechanism of combA-4P. The study suggests that if an antivascular mechanism can be demonstrated in humans, combination chemotherapy should be rapidly assessed in a clin. setting.

IT **117048-59-6**, Combretastatin A-4
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(combination chemotherapy with combretastatin A-4 phosphate and 5-fluorouracil in an exptl. murine colon adenocarcinoma)

RN 117048-59-6 CAPLUS
CN Phenol, 2-methoxy-5-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



REFERENCE COUNT: 15 THERE ARE 15 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

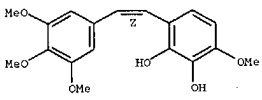
L24 ANSWER 84 OF 157 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2000:173533 CAPLUS
DOCUMENT NUMBER: 132:345465
TITLE: Bioactive Compounds from Combretum erythrophyllum
AUTHOR(S): Schwikkard, Sianne; Zhou, Bing-Nan; Glass, Thomas E.; Sharp, Jessica L.; Mattern, Michael R.; Johnson, Randall K.; Kingston, David G. I.
CORPORATE SOURCE: Department of Chemistry, Virginia Polytechnic Institute and State University, Blacksburg, VA, 24061-0212, USA
SOURCE: Journal of Natural Products (2000), 63(4), 457-460
CODEN: JNPRDF; ISSN: 0163-3864
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English

AB A methanol ext. of Combretum erythrophyllum showed inhibitory bioactivities in a yeast-based microtiter assay for DNA-damaging agents. Bioassay-guided fractionation of this ext. yielded two known bioactive compds., combretastatin A-1 and (-)-combretastatin, and two new bioactive glucosides, combretastatin A-1 2'-.beta.-D-glucoside and combretastatin B-1 2'-.beta.-D-glucoside. The structures of the new compds. were assigned by 1H and 13C NMR, DEPT, HMQC, and HMBC spectra.

IT **109971-63-3P**, Combretastatin A-1 **156085-79-9P**
RL: BAC (Biological activity or effector, except adverse); BOC (Biological occurrence); BSU (Biological study, unclassified); PRP (Properties); PUR (Purification or recovery); SPN (Synthetic preparation); BIOL (Biological study); OCCU (Occurrence); PREP (Preparation)
(isolation of bioactive compds. from Combretum erythrophyllum)

RN 109971-63-3 CAPLUS
CN 1,2-Benzenediol, 3-methoxy-6-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

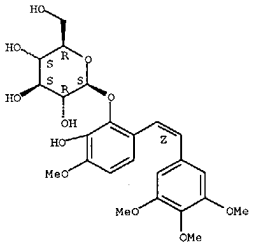
Double bond geometry as shown.



RN 156085-79-9 CAPLUS
CN .beta.-D-Glucopyranoside, 2-hydroxy-3-methoxy-6-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]phenyl (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).
Double bond geometry as shown.

L24 ANSWER 84 OF 157 CAPLUS COPYRIGHT 2003 ACS (Continued)



REFERENCE COUNT: 16 THERE ARE 16 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

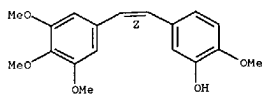
L24 ANSWER 85 OF 157 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2000:135956 CAPLUS
DOCUMENT NUMBER: 132:302959
TITLE: Multiple Flexible Alignment with SEAL: A Study of Molecules Acting on the Colchicine Binding Site
AUTHOR(S): Feher, Miklos; Schmidt, Jonathan M.
CORPORATE SOURCE: Nanodesign Inc., Guelph, ON, N1G 4Y5, Can.
SOURCE: Journal of Chemical Information and Computer Sciences (2000), 40(2), 495-502
CODEN: JCISD8; ISSN: 0095-2338
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English

AB An extension of the steric and electrostatic alignment alignment (SEAL) method (MultiSEAL) is described that allows the overlay of multiple mols. and conformations. The method is well-suited for the systematic study of possible alignments, also revealing information about the conformational energies assocd. with a given overlay. It has been tested on three examples: angiotensin II antagonists, 5-HT3 antagonists, and dopaminergic compds. The utility of the method is further demonstrated in an anal. of mols. that putatively bind to the colchicine site of tubulin. On the basis of its overlay with colchicine, allocolchicine, 2-methoxy-5-(2',3',4'-trimethoxyphenyl)tropone, and combretastatin A-4, it appears that 2-methoxyestradiol (2-ME) is unlikely to fit the colchicine site properly. The weak antimitotic activity of 2-ME may be explained by its partial fit in the site.

IT **117048-59-6**, Combretastatin A-4
RL: BPR (Biological process); BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study); PROC (Process)
(multiple flexible alignment with SEAL in study of mols. acting on colchicine binding site)

RN 117048-59-6 CAPLUS
CN Phenol, 2-methoxy-5-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

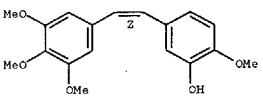
Double bond geometry as shown.



REFERENCE COUNT: 32 THERE ARE 32 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L24 ANSWER 86 OF 157 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2000:127298 CAPLUS
DOCUMENT NUMBER: 133:68491
TITLE: The new tubulin-inhibitor combretastatin A-4 enhances thermal damage in the BT4An rat glioma
AUTHOR(S): Eikesdal, H. P.; Schem, B.-C.; Mella, O.; Dahl, O.
CORPORATE SOURCE: Haukeland Hospital, Department of Oncology, University of Bergen, Bergen, Norway
SOURCE: International Journal of Radiation Oncology, Biology, Physics (2000), 46(3), 645-652
CODEN: IOBPD3; ISSN: 0360-3016
PUBLISHER: Elsevier Science Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The toxicity of combretastatin A-4 disodium phosphate (CA-4) and its vascular effects in the s.c. (s.c.) BT4An rat glioma were investigated, and addnl., the tumor response of CA-4 combined with hyperthermia was detd. For assessment of drug toxicity, rats were given 50, 75, or 100 mg/kg CA-4 and followed by daily registration of wt. and side effects. Interstitial tumor blood flow was detd. by laser Doppler flowmetry in rats injected with 50 mg/kg CA-4. In the tumor response study the authors administered CA-4 50 mg/kg alone or combined with hyperthermia (water bath 44.degree. for 60 min) 0 or 3 h later. The authors found that CA-4, at a well-tolerated dose of 50 mg/kg, induced a considerable time-dependent decrease in the tumor blood flow. Tumor blood flow was reduced by 47-55% during the 1st 110 min after injecting CA-4, and thereafter remained decreased until the measurements were terminated. Administering CA-4 3 h before hyperthermia yielded the best tumor response and increased tumor growth time significantly compared with simultaneous administration of CA-4 and hyperthermia ($p = 0.03$). Interestingly, CA-4 alone did not influence tumor growth. Thus, CA-4 induces a gradual redn. in tumor blood flow which can be exploited to sensitize the BT4An tumor for hyperthermia.
IT **117048-59-6**, Combretastatin A-4
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(combretastatin A-4 combined with hyperthermia enhanced damage in the BT4An glioma)
RN 117048-59-6 CAPLUS
CN Phenol, 2-methoxy-5-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

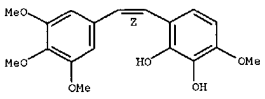
Double bond geometry as shown.



REFERENCE COUNT: 44 THERE ARE 44 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L24 ANSWER 87 OF 157 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2000:100968 CAPLUS
DOCUMENT NUMBER: 132:234333
TITLE: Uteroactive constituents from Combretum kraussii
AUTHOR(S): Brookes, K. Bridget; Doudoukina, Olga V.; Katsoulis, Lynn C.; Veale, D. Joy H.
CORPORATE SOURCE: Technikon Mangosuthu, Jacobs, 4026, S. Afr.
SOURCE: South African Journal of Chemistry (1999), 52(4), 127-132
CODEN: SAJCDG; ISSN: 0379-4350
PUBLISHER: South African Chemical Institute
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The authors have established that certain exts. of Combretum kraussii Hochst roots cause contractions in isolated rat uterine tissue, and have purified the most active uterotonic components. The mode of action of the various exts./components on isolated rat uterus falls into three different categories. The activity of crude exts. from leaves and branches of C. erythrophyllum (Burch.) Sond. and C. kraussii Hochst was also measured. The following compds. were identified from root exts.: combretastatin, combretastatin A-1 and combretastatin B-1, as well as the corresponding 2-O-.beta.-D-glucosides of the latter two combretastatins, .beta.-sitosterol, ellagic acid and the di- and tri-Me ethers of ellagic acid. This is the first report of the occurrence of combretastatin and ellagic acid derivs. in this Combretum species.
IT **109971-63-3**, Combretastatin A-1 **156085-79-9**
RL: BAC (Biological activity or effector, except adverse); BOC (Biological occurrence); BSU (Biological study, unclassified); BIOL (Biological study); OCCU (Occurrence)
(uteroactive constituents from Combretum kraussii)
RN 109971-63-3 CAPLUS
CN 1,2-Benzenediol, 3-methoxy-6-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

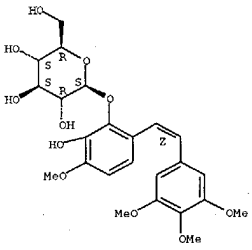
Double bond geometry as shown.



RN 156085-79-9 CAPLUS
CN .beta.-D-Glucopyranoside, 2-hydroxy-3-methoxy-6-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]phenyl (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).
Double bond geometry as shown.

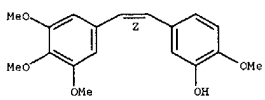
L24 ANSWER 87 OF 157 CAPLUS COPYRIGHT 2003 ACS (Continued)



REFERENCE COUNT: 15 THERE ARE 15 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L24 ANSWER 88 OF 157 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2000:97483 CAPLUS
DOCUMENT NUMBER: 132:260306
TITLE: Evaluation of antivascular and antimitotic effects of tubulin binding agents in solid tumor therapy
AUTHOR(S): Nihei, Yukio; Suzuki, Manabu; Okano, Akira; Tsuji, Takashi; Akiyama, Yukio; Tsuruo, Takashi; Saito, Sachiko; Hori, Katsuyoshi; Sato, Yasufumi
CORPORATE SOURCE: Pharmaceutical Research Laboratories, Ajinomoto Co., Inc., Kawasaki, 210-8681, Japan
SOURCE: Japanese Journal of Cancer Research (1999), 90(12), 1387-1396
CODEN: JJCREP; ISSN: 0910-5050
PUBLISHER: Japanese Cancer Association
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Tubulin binding agents (TBAs) reduce tumor perfusion and inhibit mitosis of tumor cells in solid tumors, but it is not clear which effects contribute to the suppression of solid tumor growth. We evaluated the antivascular and antimitotic effects of several TBAs, combretastatin A-4 (CS A-4) phosphate, AC-7700, a novel CS A-4 deriv., colchicine, E7010, and vinblastine, on s.c. (s.c.) murine colon26 adenocarcinoma (c26). Tolerable doses of vinblastine and E7010 strongly inhibited tumor growth and induced mitotic arrest of tumor cells without affecting tumor perfusion. Colchicine had no effect on tumor growth and perfusion. When the injected dose was increased to the lethal range, however, these drugs markedly reduced tumor perfusion and caused necrosis of tumor tissue. Within the tolerable dose range, AC-7700 both strongly suppressed tumor growth and reduced tumor perfusion, and CS A-4 phosphate also exhibited a moderate antivascular effect. To evaluate the contribution of antivascular activity of TBAs to tumor growth suppression, excluding their direct cytotoxic effect on tumor cells, we established c26/acr, which is resistant to TBAs in vitro. Although E7010 showed a reduced suppressive effect on s.c. c26/acr tumor growth as compared with its effect on wild-type c26, AC-7700 remained potent against both cell lines. These results indicate that TBAs exert antivascular and antimitotic effects on solid tumors with marked differently ED ranges from agent to agent, and that the antivascular effect of TBAs inhibits solid tumor growth independently of the direct cytotoxic effect on tumor cells.
IT **117048-59-6**, Combretastatin A-4
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(evaluation of antivascular and antimitotic effects of tubulin binding agents in solid tumor therapy)
RN 117048-59-6 CAPLUS
CN Phenol, 2-methoxy-5-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

Double bond geometry as shown.

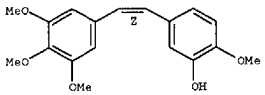


REFERENCE COUNT: 25 THERE ARE 25 CITED REFERENCES AVAILABLE FOR THIS

L24 ANSWER 88 OF 157 CAPLUS COPYRIGHT 2003 ACS (Continued)
RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L24 ANSWER 89 OF 157 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2000:56669 CAPLUS
DOCUMENT NUMBER: 132:303079
TITLE: In vivo and in vitro evaluation of combretastatin A-4 and its sodium phosphate prodrug
AUTHOR(S): Grosios, K.; Holwell, S. E.; McGown, A. T.; Pettit, G. R.; Bibby, M. C.
CORPORATE SOURCE: Clinical Oncology Unit, University of Bradford, Bradford, BD7 1DP, UK
SOURCE: British Journal of Cancer (1999), 81(8), 1318-1327
CODEN: BJCAAI; ISSN: 0007-0920
PUBLISHER: Churchill Livingstone
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The antitumor effects and mechanism of action of combretastatin A-4 and its prodrug, combretastatin A-4 disodium phosphate, were examd. in s.c. and orthotopically transplanted exptl. colon tumors in mice. Addnl., the ability of these compds. to directly interfere with endothelial cell behavior was also examd. in human vein endothelial cell (HUVEC) cultures. Combretastatin A-4 (150 mg/kg, i.p.) and its water-sol. prodrug (100 mg/kg, i.p.) caused almost complete vascular shutdown (after 4 h), extensive hemorrhagic necrosis which started 1 h after treatment and significant tumor growth delay in MAC 15A s.c. colon tumors. Similar vascular effects were obtained in MAC 15 orthotopic tumors and SW620 human colon tumor xenografts treated with the prodrug. More importantly, in the orthotopic models, necrosis was seen in vascularized metastatic deposits but not in avascular secondary deposits. The possible mechanism giving rise to these effects was examd. in HUVEC cells. Here, cellular networks formed in type I calf-skin collagen layers, and these networks were completely disrupted when the layers were incubated with a noncytotoxic concn. of combretastatin A-4 or its prodrug. This effect started after 4 h and was complete by 24 h. The same noncytotoxic concns. resulted in disorganization of F-actin and .beta.-tubulin 1 h after treatment. In conclusion, combretastatin A-4 and its prodrug caused extensive necrosis in MAC 15A s.c. and orthotopic colon cancer and metastases, resulting in antitumor effects. Necrosis was not seen in avascular tumor nodules, suggesting a vascular mechanism of action.
IT **117048-59-6**, Combretastatin A4
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(colon cancer inhibition by combretastatin A-4 and its sodium phosphate prodrug)
RN 117048-59-6 CAPLUS
CN Phenol, 2-methoxy-5-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

Double bond geometry as shown.

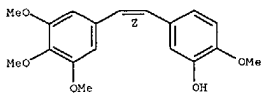


L24 ANSWER 89 OF 157 CAPLUS COPYRIGHT 2003 ACS (Continued)

REFERENCE COUNT: 39 THERE ARE 39 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

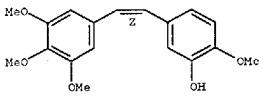
L24 ANSWER 90 OF 157 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1999:707755 CAPLUS
DOCUMENT NUMBER: 132:35492
TITLE: Synthesis and biological evaluation of novel photoaffinity labeling reagents and nitrogen-containing compounds modeled after combretastatin a-4
AUTHOR(S): Mejia, Maria Del Pilar
CORPORATE SOURCE: Baylor Univ., Waco, TX, USA
SOURCE: (1999) 266 pp. Avail.: UMI, Order No. DA9925082
From: Diss. Abstr. Int., B 1999, 60(5), 2137
DOCUMENT TYPE: Dissertation
LANGUAGE: English
AB Unavailable
IT **117048-59-6**, Combretastatin a4
RL: MSC (Miscellaneous)
(synthesis and biol. evaluation of novel photoaffinity labeling reagents and nitrogen-contg. compds. modeled after combretastatin a4)
RN 117048-59-6 CAPLUS
CN Phenol, 2-methoxy-5-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



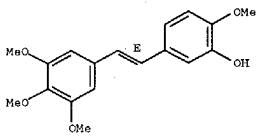
L24 ANSWER 91 OF 157 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1999:572221 CAPLUS
DOCUMENT NUMBER: 131:336876
TITLE: The synthesis of (E)- and (Z)-combretastatins A-4 and a phenanthrene from Combretum caffrum
AUTHOR(S): Lawrence, Nicholas J.; Ghani, Fazni Abdul; Hepworth, Lucy A.; Hadfield, John A.; McGown, Alan T.; Pritchard, Robin G.
CORPORATE SOURCE: Department Chemistry, UMIST, Manchester, M60 1QD, UK
SOURCE: Synthesis (1999), (9), 1656-1660
CODEN: SYNTBF; ISSN: 0039-7881
PUBLISHER: Georg Thieme Verlag
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 131:336876
AB The synthesis of the trans-stilbene (E)-combretastatin A-4 was achieved via a Horner-Wittig reaction of 3,4,5-(MeO)3C6H2CH2P(O)Ph2. The anticancer drug (Z)-combretastatin A-4 was prepd. by the hydroboration/protonation of a diaryl alkyne (no data).
IT **117048-59-6P**, Combretastatin A-4 **117048-62-1P**, E-Combretastatin A-4
RL: SPN (Synthetic preparation); PREP (Preparation)
(prepn. of combretastatin A-4 and Combretum phenanthrene)
RN 117048-59-6 CAPLUS
CN Phenol, 2-methoxy-5-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



RN 117048-62-1 CAPLUS
CN Phenol, 2-methoxy-5-[(1E)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

Double bond geometry as shown.

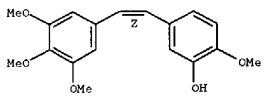


REFERENCE COUNT: 22 THERE ARE 22 CITED REFERENCES AVAILABLE FOR THIS

L24 ANSWER 91 OF 157 CAPLUS COPYRIGHT 2003 ACS (Continued)
RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L24 ANSWER 92 OF 157 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1999:567462 CAPLUS
DOCUMENT NUMBER: 132:180406
TITLE: Synthesis of combretastatin A-4 derivatives, phenstatin, phakellistatin 5, and an approach to dolastatin 17
AUTHOR(S): Toki, Brian Eric
CORPORATE SOURCE: Arizona State Univ., Tempe, AZ, USA
SOURCE: (1999) 369 pp. Avail.: UMI, Order No. DA9924211
From: Diss. Abstr. Int., B 1999, 60(3), 1093
DOCUMENT TYPE: Dissertation
LANGUAGE: English
AB Unavailable
IT **117048-59-6P**, Combretastatin a-4
RL: SPN (Synthetic preparation); PREP (Preparation)
(synthesis of combretastatin a-4 derivs., phenstatin, phakellistatin 5, and approach to dolastatin 17)
RN 117048-59-6 CAPLUS
CN Phenol, 2-methoxy-5-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



L24 ANSWER 93 OF 157 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1999:529049 CAPLUS
DOCUMENT NUMBER: 131:175072
TITLE: Hydroxylation-activated drug release, and prodrug preparation
INVENTOR(S): Potter, Gerard Andrew; Patterson, Lawrence Hylton; Burke, Michael Danny
PATENT ASSIGNEE(S): De Montfort University, UK
SOURCE: PCT Int. Appl., 53 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

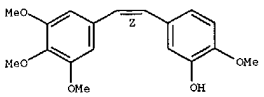
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9940944	A2	19990819	WO 1999-GB416	19990210
WO 9940944	A3	19990923		
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
GB 2334256	A1	19990818	GB 1998-2957	19980212
US 2002037296	A1	20020328	US 1998-115016	19980714
CA 2319837	AA	19990819	CA 1999-2319837	19990210
AU 9925315	A1	19990830	AU 1999-25315	19990210
EP 1069915	A2	20010124	EP 1999-905005	19990210
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				

PRIORITY APPLN. INFO.: GB 1998-2957 A 19980212
US 1998-115016 A 19980714
WO 1999-GB416 W 19990210

OTHER SOURCE(S): MARPAT 131:175072
AB The invention concerns prodrugs whose arom. oxidn., particularly their enzymic arom. hydroxylation, results in their activation by the release of a drug moiety. It particularly concerns antitumor prodrugs and those which are specifically activated by the hydroxylation activity of the P 450 enzyme CYP1B1. Also provided are methods of detection of arom. oxidn. activity. Prepn. of prodrugs of the invention is described.
IT **117048-59-6**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(biol.; hydroxylation activated drug release, and prodrug prepn.)
RN 117048-59-6 CAPLUS
CN Phenol, 2-methoxy-5-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

Double bond geometry as shown.

L24 ANSWER 93 OF 157 CAPLUS COPYRIGHT 2003 ACS (Continued)



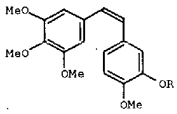
L24 ANSWER 94 OF 157 CAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 1999:451301 CAPLUS
DOCUMENT NUMBER: 131:73507
TITLE: Preparation and formulation of combretastatin A4 prodrugs and their trans-isomers for use as antitumor agents
INVENTOR(S): Pettit, George R.; Rhodes, Monte R.
PATENT ASSIGNEE(S): Arizona State University, USA
SOURCE: PCT Int. Appl., 55 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9935150	A1	19990715	WO 1999-US419	19990108
W: CA, JP, US				
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
CA 2314238	AA	19990715	CA 1999-2314238	19990108
EP 1045853	A1	20001025	EP 1999-902121	19990108
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, PT, IE, FI				
JP 2002500227	T2	20020108	JP 2000-527548	19990108

PRIORITY APPLN. INFO.: US 1998-71070P P 19980109
US 1998-111531P P 19981209
WO 1999-US419 W 19990108

GI



I

AB Combretastatin A4 I (R = H) and analogous phosphate prodrugs I [R = PO(OR1)OR2; R1, R2 = H, Na, Ca, Cs, Li, Mg, Mn, Zn, imidazole, morpholine, piperazine piperidine, pyrazole, pyridine, adenosine, cinchonine, glucosamine quinine, quinidine, tetracycline, verapamil; R1 = R2 = H, benzyl] and (E)-Combretastatin A4 phosphate analogs were prepd. and formulated for use as water sol. antineoplastic agents. Thus, combretastatin A4 was reacted with dibenzyl phosphite to give dibenzyl ester I [R = P(O)(OCH2Ph)2] in 98% yield. Also, combretastatin A4 was converted to the sodium phosphate salt I [R = PO3HNa] via the formation of the silylethyl ester I [R = P(O)(OCH2CH2SiMe3)2]. The combretastatin A4 phosphate esters were tested for antitumor activity against a variety of cancer cell lines and were also tested for antimicrobial activity against bacterial and fungal strains.

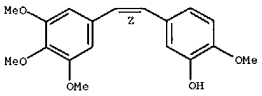
IT **117048-59-6**, Combretastatin A4 **117048-62-1**, (E)-Combretastatin A4

L24 ANSWER 94 OF 157 CAPLUS COPYRIGHT 2003 ACS (Continued)

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); RCT (Reactant); THU (Therapeutic use); BIOL (Biological study); RACT (Reactant or reagent); USES (Uses)
(prepn. and formulation of combretastatin A4 prodrugs and their trans-isomers for use as antitumor agents)

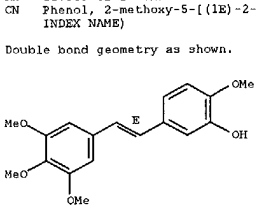
RN 117048-59-6 CAPLUS
CN Phenol, 2-methoxy-5-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



RN 117048-62-1 CAPLUS
CN Phenol, 2-methoxy-5-[(1E)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L24 ANSWER 95 OF 157 CAPLUS COPYRIGHT 2003 ACS

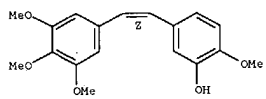
ACCESSION NUMBER: 1999:449666 CAPLUS
DOCUMENT NUMBER: 132:90067
TITLE: Examples of adjuvant treatment enhancing the antitumor effect of photodynamic therapy
AUTHOR(S): Korbelik, Mladen; Cecic, Ivana; Sun, Jinghai; Chaplin, David J.
CORPORATE SOURCE: British Columbia Cancer Agency, Vancouver, BC, Can.
SOURCE: Proceedings of SPIE-The International Society for Optical Engineering (1999), 3592(Optical Methods for Tumor Treatment and Detection: Mechanisms and Techniques in Photodynamic Therapy VIII), 65-72
CODEN: PSISDG; ISSN: 0277-786X
PUBLISHER: SPIE-The International Society for Optical Engineering
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A review with 51 refs. Strategies for improving the clin. efficacy of photodynamic therapy (PDT) in treatment of solid cancers include applications of different types of adjuvant treatments in addn. to this modality that may result in superior therapeutic outcome. Examples of such an approach investigated using mouse tumor models are presented in this report. It is shown that the cures of PDT treated s.c. tumors can be substantially improved by adjuvant therapy with: metoclopramide (enhancement of cancer cell apoptosis), combretastatin A-4 (selective destruction of tumor neovasculature), Roussin's Black Salt (light activated tumor localized release of nitric oxide), or dendritic cell-based adoptive immunotherapy (immune rejection of treated tumor).

IT **117048-59-6**, Combretastatin A-4
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(adjuvant treatment enhancing antitumor effect of photodynamic therapy)

RN 117048-59-6 CAPLUS
CN Phenol, 2-methoxy-5-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



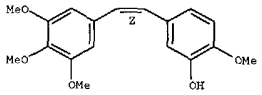
REFERENCE COUNT: 51 THERE ARE 51 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L24 ANSWER 96 OF 157 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1999:297331 CAPLUS
DOCUMENT NUMBER: 130:342996
TITLE: Heparin-binding growth factor derivatives
INVENTOR(S): Gallagher, John Thomas; Pye, David Alexander
PATENT ASSIGNEE(S): Cancer Research Campaign Technology Limited, UK
SOURCE: PCT Int. Appl., 76 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9921588	A1	19990506	WO 1998-GB3201	19981028
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
AU 9910391	A1	19990517	AU 1999-10391	19981028
PRIORITY APPLN. INFO.:			GB 1997-22604	19971028
			WO 1998-GB3201	19981028

AB Covalently crosslinked conjugates of heparin-binding growth factors and heparin or heparan sulfate (HS) oligosaccharides which can be used as therapeutic agents for modulating the biol. activity of such growth factors and/or for targeted delivery of drugs are disclosed. Such conjugates enable exogenous growth factors to be administered to mammals for medical treatment so as either to promote or to inhibit growth factor biol. activity, or to act as targeting carriers of drug mols. linked thereto. Covalent crosslinked conjugates of HS oligosaccharides and basic fibroblast growth factor were prepd.
IT **117048-59-6D**, Combretastatin, derivs.
RL: RCT (Reactant); THU (Therapeutic use); BIOL (Biological study); RACT (Reactant or reagent); USES (Uses)
(heparin-binding growth factor derivs.)
RN 117048-59-6 CAPLUS
CN Phenol, 2-methoxy-5-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

Double bond geometry as shown.

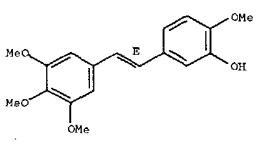


REFERENCE COUNT: 8 THERE ARE 8 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L24 ANSWER 96 OF 157 CAPLUS COPYRIGHT 2003 ACS (Continued)

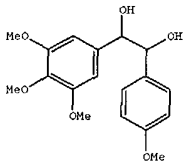
L24 ANSWER 97 OF 157 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1999:284035 CAPLUS
DOCUMENT NUMBER: 131:82669
TITLE: Antineoplastic agents 393. Synthesis of the trans-isomer of combretastatin A-4 prodrug
AUTHOR(S): Pettit, George R.; Rhodes, Monte R.; Herald, Delbert L.; Chaplin, Dai J.; Stratford, Michael R. L.; Hamel, Ernest; Pettit, Robin K.; Chapuis, Jean-Charles; Oliva, Deanna
CORPORATE SOURCE: Cancer Research Institute and Department of Chemistry, Arizona State University, Tempe, AZ, 85287-2494, USA
SOURCE: Anti-Cancer Drug Design (1998), 13(8), 981-993
CODEN: ACDDEA; ISSN: 0266-9536
PUBLISHER: Oxford University Press
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The (E)-stilbene isomer (2a) of the (Z)-combretastatin A-4 prodrug (1b) was efficiently prepd. from (E)-combretastatin A-4 by a reaction sequence employing phosphorylation (dibenzyl chlorophosphite), cleavage (trimethyliodosilane) of the benzyl ester and reaction of the resulting phosphoric acid with sodium methoxide. The sodium phosphate product (2c) was also found to be an important side-product, presumably from iodine-catalyzed isomerization, when the analogous synthetic route was used to obtain the combretastatin A-4 prodrug (1b). The phosphoric acid precursor of prodrug 1b derived from (Z)-combretastatin A-4 (1a) was converted into a series of metal cation and ammonium cation salts to evaluate effects on human cancer cell growth, antimicrobial activities and soly. behavior.
IT **117048-62-1**
RL: RCT (Reactant); RACT (Reactant or reagent)
(synthesis of the antitumor trans-isomer of combretastatin A-4 prodrug)
RN 117048-62-1 CAPLUS
CN Phenol, 2-methoxy-5-[(1E)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



REFERENCE COUNT: 12 THERE ARE 12 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L24 ANSWER 98 OF 157 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1999:282459 CAPLUS
DOCUMENT NUMBER: 131:129806
TITLE: Design and synthesis of novel antimitotic agents for colchicine binding site of tubulin
AUTHOR(S): Nishikawa, A.; Shirai, R.; Onoda, T.; Takahashi, M.; Okabe, T.; Koiso, Y.; Iwasaki, S.
CORPORATE SOURCE: Institute of Molecular and Cellular Biosciences, The University of Tokyo, Tokyo, Japan
SOURCE: Tennen Yuki Kagobutsu Toronkai Koen Yoshishu (1997), 39th, 457-462
CODEN: TYKYDS
PUBLISHER: Nippon Kagakkai
DOCUMENT TYPE: Journal
LANGUAGE: Japanese
GI

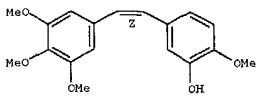


I

AB Combretastatin A-4 isolated from Combretum caffrum is reported to be one of the most potent antimitotic agents which strongly inhibits the polymn. of brain tubulin by binding to the colchicine site (CLC site). Common elements can be found among the structures of the active combretastatins congeners and of other well-known CLC site ligands such as colchicine, steganacin and podophyllotoxin. It has been proposed that CLC site ligands retain optically active conformation at the binding site of tubulin. Although Combretastatin A-4 is not a chiral mol., it is expected to exist as chiral conformer induced by the binding to tubulin. A series of conformationally restricted heterocyclic combretastatin analogs have been synthesized from (R,R)-I, (S, S)-I and (RS,SR)-I and their inhibitory activity of microtubule assembly was evaluated. (4S,5S)-4-(4-Methoxyphenyl)-5-(3,4,5-trimethoxyphenyl)-1,3-dioxolane showed moderate antimitotic activity while its enantiomer and other diastereomers synthesized were inactive. Curacin A is a powerful antimitotic agent isolated from an Caribbean cyanobacterium Lyngbya majuscula in 1994. Although curacin A binds to CLC site as combretastatin A-4 does, there is no structural similarity to other known CLC site ligands. A variety of side chain analogs of curacin A were synthesized and the effect to in vitro microtubule polymn. was examd. However, compds. synthesized showed weak or no activity suggesting that the side chain was restrictly recognized by microtubule proteins.
IT **117048-59-6**, Combretastatin A-4
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(design and synthesis of novel antimitotic agents for colchicine binding site of tubulin)
RN 117048-59-6 CAPLUS

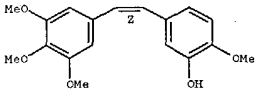
L24 ANSWER 98 OF 157 CAPLUS COPYRIGHT 2003 ACS (Continued)
CN Phenol, 2-methoxy-5-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



L24 ANSWER 99 OF 157 CAPLUS COPYRIGHT 2003 ACS (Continued)
INDEX NAME)

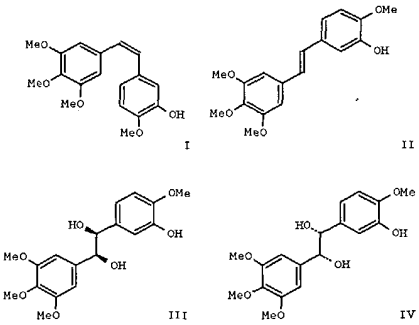
Double bond geometry as shown.



REFERENCE COUNT: 43 THERE ARE 43 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L24 ANSWER 99 OF 157 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1999:241795 CAPLUS
DOCUMENT NUMBER: 131:39356
TITLE: Combretastatin A-4 phosphate as a tumor vascular-targeting agent: early effects in tumors and normal tissues
AUTHOR(S): Tozer, Gillian M.; Prise, Vivien E.; Wilson, John; Locke, Rosalind J.; Vojnovic, Borivoj; Stratford, Michael R. L.; Dennis, Madeleine F.; Chaplin, David J.
CORPORATE SOURCE: Tumor Microcirculation Group, Gray Laboratory Cancer Research Trust, Mount Vernon Hospital, Northwood, HA6 2JR, UK
SOURCE: Cancer Research (1999), 59(7), 1626-1634
CODEN: CNREA8; ISSN: 0008-5472
PUBLISHER: AACR Subscription Office
DOCUMENT TYPE: *Journal*
LANGUAGE: English
AB The potential for tumor vascular-targeting by using the tubulin destabilizing agent disodium combretastatin A-4 3-O-phosphate (CA-4-P) was assessed in a rat system. This approach aims to shut down the established tumor vasculature, leading to the development of extensive tumor cell necrosis. The early vascular effects of CA-4-P were assessed in the s.c. implanted P22 carcinosarcoma and in a range of normal tissues. Blood flow was measured by the uptake of radiolabeled iodoantipyrine, and quant. autoradiog. was used to measure spatial heterogeneity of blood flow in tumor sections. CA-4-P (100 mg/kg i.p.) caused a significant increase in mean arterial blood pressure at 1 and 6 h after treatment and a very large decrease in tumor blood flow, which-by 6 h-was reduced approx. 100-fold. The spleen was the most affected normal tissue with a 7-fold redn. in blood flow at 6 h. Calcns. of vascular resistance revealed some vascular changes in the heart and kidney for which there were no significant changes in blood flow. Quant. autoradiog. showed that CA-4-P increased the spatial heterogeneity in tumor blood flow. The drug affected peripheral tumor regions less than central regions. Administration of CA-4-P (30 mg/kg) in the presence of the nitric oxide synthase inhibitor, N,omega.-nitro-L-arginine Me ester, potentiated the effect of CA-4-P in tumor tissue. The combination increased tumor vascular resistance 300-fold compared with less than 7-fold for any of the normal tissues. This shows that tissue prodn. of nitric oxide protects against the damaging vascular effects of CA-4-P. Significant changes in tumor vascular resistance could also be obtained in isolated tumor perfusions using a cell-free perfusate, although the changes were much less than those obsd. in vivo. This shows that the action of CA-4-P includes mechanisms other than those involving red cell viscosity, intravascular coagulation, and neutrophil adhesion. The uptake of CA-4-P and combretastatin A-4 (CA-4) was more efficient in tumor than in skeletal muscle tissue and dephosphorylation of CA-4-P to CA-4 was faster in the former. These results are promising for the use of CA-4-P as a tumor vascular-targeting agent.
IT **117048-59-6**, Combretastatin A-4
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(combretastatin A-4 phosphate as a tumor vascular-targeting agent)
RN 117048-59-6 CAPLUS
CN Phenol, 2-methoxy-5-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA

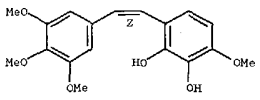
L24 ANSWER 100 OF 157 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1999:222768 CAPLUS
DOCUMENT NUMBER: 131:31823
TITLE: *Antineoplastic Agents. 410. Asymmetric Hydroxylation of trans-Combretastatin A-4*
AUTHOR(S): Pettit, George R.; Toki, Brian E.; Herald, Delbert L.; Boyd, Michael R.; Hamel, Ernest; Pettit, Robin K.; Chapuis, J. Charles
CORPORATE SOURCE: Cancer Research Institute and Department of Chemistry, Arizona State University, Tempe, AZ, 85287-2404, USA
SOURCE: Journal of Medicinal Chemistry (1999), 42(8), 1459-1465
CODEN: JMCMAR; ISSN: 0022-2623
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 131:31823
GI



AB The South African willow tree Combretum caffrum has yielded a no. of *potent cancer cell growth inhibitors. The present* SAR studies of the antineoplastic agent combretastatin A-4 (I) were focused mainly on the olefinic bridge to det. the effects on cancer cell growth and, potentially, to better define the combretastatin A-4 binding site on tubulin. The geometric trans-isomer II of combretastatin A-4 was converted to the (1S,2S)- and (1R,2R)-vicinal diols III and IV, resp., under Sharpless' asym. dihydroxylation conditions. Cancer cell line testing showed the (1S,2S)-diol III to be more potent than its enantiomer IV. Diol III weakly inhibited tubulin polymn. (IC50 = 22 .mu.M, vs. 1.2 .mu.M for combretastatin A-4), while IV was inactive (IC50 > 40 .mu.M). Esterification of either stereoisomer at the diol and/or phenolic

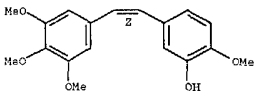
L24 ANSWER 100 OF 157 CAPLUS COPYRIGHT 2003 ACS (Continued)
positions resulted in elimination of inhibitory activity.
IT **109971-63-3**, Combretastatin A-1 **117048-59-6**, Combretastatin A-4 **117048-62-1**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(prepn. of antineoplastic agents via asym. vicinal hydroxylation of trans-Combretastatin A-4)
RN 109971-63-3 CAPLUS
CN 1,2-Benzenediol, 3-methoxy-6-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



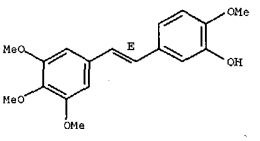
RN 117048-59-6 CAPLUS
CN Phenol, 2-methoxy-5-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



RN 117048-62-1 CAPLUS
CN Phenol, 2-methoxy-5-[(1E)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

Double bond geometry as shown.

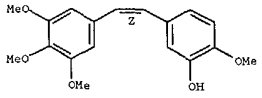


REFERENCE COUNT: 27 THERE ARE 27 CITED REFERENCES AVAILABLE FOR THIS

L24 ANSWER 100 OF 157 CAPLUS COPYRIGHT 2003 ACS (Continued)
RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L24 ANSWER 101 OF 157 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1999:129772 CAPLUS
DOCUMENT NUMBER: 131:99313
TITLE: Positron emission tomography of murine liver metastases and the effects of treatment by combretastatin A-4
AUTHOR(S): Zhao, Shai; Moore, James V.; Waller, Michael L.; McGown, Alan T.; Hadfield, John A.; Pettit, George R.; Hastings, David L.
CORPORATE SOURCE: North West Medical Physics, Christie Hospital (NHS) Trust, Manchester, UK
SOURCE: European Journal of Nuclear Medicine (1999), 26(3), 231-238
CODEN: EJNMD9; ISSN: 0340-6997
PUBLISHER: Springer-Verlag
DOCUMENT TYPE: Journal
LANGUAGE: English
AB There are major potential advantages in non-invasive measurement of preclin. tumor biol. and therapeutic response in clin. relevant, internal body sites, notably the ability to follow outcome in individual animals rather than averaging results from groups. We have exploited positron emission tomog. (PET) to det. the feasibility of detecting liver *metastases in B6D2F1 mice using fluorine-18 fluorodeoxyglucose ([18F]FDG)* both before and after treatment by the novel cytotoxic agent, combretastatin A-4. The normal distribution of [18F]FDG in the absence of disease was characteristic, with clear delineation of the brain, the heart and the urinary bladder in all studies. In untreated mice with liver metastases, a strong correlation (r2 = 0.98) was found between the quant. ests. of [18F]FDG uptake obtained by anal. of PET images, and those obtained from ex vivo assay of liver plus metastases excised immediately after imaging. In this first series, the effective limit of resoln. was in livers contg. a no. of small metastases (range 8-14) with a single vol. equiv. of approx. 200 mm3. PET image anal. was concordant with histol. measurements in showing that single i.p. doses of combretastatin A-4 resulted in an av. 30% vol. destruction of metastatic mass by 24 h following administration.
IT **117048-59-6**, Combretastatin A-4
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
([18F]FDG PET detecting of liver metastases before and after treatment with combretastatin A-4)
RN 117048-59-6 CAPLUS
CN Phenol, 2-methoxy-5-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



REFERENCE COUNT: 22 THERE ARE 22 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L24 ANSWER 102 OF 157 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1999:89966 CAPLUS
DOCUMENT NUMBER: 130:261394
TITLE: Determination of combretastatin A-4 and its drug in plasma by high-performance liquid chromatography
AUTHOR(S): Stratford, Michael R. L.; Dennis, Madeleine F.
CORPORATE SOURCE: Gray Laboratory Cancer Research Trust, Mount Vernon *Hospital, Northwood/Middlesex, HA6 2JR, UK*
SOURCE: Journal of Chromatography, B: Biomedical Sciences and Applications (1999), 721(1), 77-85
CODEN: JCBBEP; ISSN: 0378-4347
PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB High-performance liq. chromatog. with both absorbance and fluoresce detn. of the potential anti-tumor agent combretastatin A-4 and its phosphate ester in murine and human plasma. The presence of different interfering peaks in the two species makes absorbance detection at 295 nm the method of choice for the mouse, and fluorescence detection (295 nm/390 nm) for human plasma. The calibration was linear over the range studied (0.01-50 .mu.M for combretastatin A-4, 0.02-200 .mu.M for combretastatin A-4 phosphate), with quantitation limits of 0.05 .mu.M for both drugs in the *mouse, and 0.05 .mu.M and 0.0125 .mu.M for the phosphate ester and free* drug, resp., in human plasma. The method should be useful for pharmacokinetic studies in the forthcoming Phase 1 clin. trial of combretastatin A-4 phosphate.
IT **117048-59-6**, Combretastatin A-4
RL: ANT (Analyte); ANST (Analytical study)
(detn. of combretastatin A-4 and drug in plasma of humans and lab. animals by high-performance liq. chromatog.)
RN 117048-59-6 CAPLUS
CN Phenol, 2-methoxy-5-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

Double bond geometry as shown.

REFERENCE COUNT: 8 THERE ARE 8 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

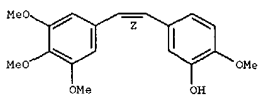
L24 ANSWER 103 OF 157 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1998:791632 CAPLUS
DOCUMENT NUMBER: 130:138888
TITLE: The synthesis of alkenes via epi-phosphonium species: 1. An Anti-Wittig elimination
AUTHOR(S): Lawrence, Nicholas J.; Muhammad, Faiz
CORPORATE SOURCE: Department of Chemistry, University of Manchester Institute of Science and Technology, Manchester, M60 1QD, UK
SOURCE: Tetrahedron (1998), 54(50), 15345-15360
CODEN: TETRAB; ISSN: 0040-4020
PUBLISHER: Elsevier Science Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 130:138888

AB *Anti-1,2-phosphinyl alcs. and their corresponding syn-isomers* upon treatment with phosphorus trichloride and triethylamine give E and Z alkenes resp., by an anti elimination. This is in marked contrast to the syn Horner-Wittig elimination of the corresponding 1,2-phosphinoyl alcs. The 1,2-phosphinyl alcs. were prepd. by the redn. of 1,2-phosphinoyl alcs. with cerium(III) chloride/lithium aluminum hydride. The anti elimination is explained by the formation of a transient epi-phosphonium species. An unexpected E-selective Horner-Wittig elimination during the cerium(III) chloride/lithium aluminum hydride redn. of a 1,2-phosphinoyl alc. in which the diphenylphosphinoyl group is adjacent to an aryl group is described. This led to the synthesis of the antimitotic agent E-combretastatin A-4. An alternative synthesis of the 1,2-phosphinyl alcs. from the corresponding phosphine-borane complex is also described.

IT **117048-59-6P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(prepn. of)

RN 117048-59-6 CAPLUS
CN Phenol, 2-methoxy-5-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



REFERENCE COUNT: 46 THERE ARE 46 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

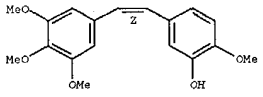
L24 ANSWER 104 OF 157 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1998:769241 CAPLUS
DOCUMENT NUMBER: 130:95419
TITLE: Semiempirical studies of ring twisting in cis-stilbene and related biomolecules
AUTHOR(S): Monaco, Regina R.; Gardiner, William C., Jr; Kirschner, Stephen
CORPORATE SOURCE: Department of Biology, New York University, New York, NY, 10003, USA
SOURCE: International Journal of Quantum Chemistry (1999), 71(1), 57-62
CODEN: IJQCB2; ISSN: 0020-7608
PUBLISHER: John Wiley & Sons, Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB *The geometric and energetic predictions of the MNDO, AM1, and SAM1 models* as they describe rotation of the dihedral angle between the plane of one of the Ph rings and the plane of the olefin core of cis-stilbene (cis-1,2-diphenylethylene) were tested for a variety of constraints. All three models predict that distortions away from the stable structure fixed by a compromise between .pi.-electron and steric repulsions lead to small (at most 1-2 kcal/mol) strain energies and geometry relaxations. Extensive peripheral substitution on the Ph rings present in a prototype natural product having the cis-stilbene structure, Combretastatin A-4 (3,4,5-trimethoxy-3'-hydroxy-4'-methoxy-(Z)-stilbene), distorted the shapes of the cis-stilbene barriers to conformation change only minimally. It is concluded that natural products having the cis-stilbene structure should be expected to interact with other biomols. as if the Ph twists are barrier free.

IT **117048-59-6**, Combretastatin A-4
RL: PEP (Physical, engineering or chemical process); PRP (Properties); PROC (Process)
(semiempirical studies of ring twisting in cis-stilbene and related biomols.)

RN 117048-59-6 CAPLUS
CN Phenol, 2-methoxy-5-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



REFERENCE COUNT: 20 THERE ARE 20 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

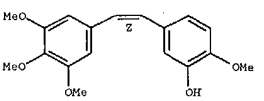
L24 ANSWER 105 OF 157 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1998:671802 CAPLUS
DOCUMENT NUMBER: 130:32771
TITLE: *Induction of apoptosis in proliferating* human endothelial cells by the tumor-specific antiangiogenesis agent combretastatin A-4
AUTHOR(S): Iyer, Sudha; Chaplin, Dai J.; Rosenthal, Dean S.; Boulares, A. Hamid; Li, Lu-Yuan; Smulson, Mark E.
CORPORATE SOURCE: Department of Biochemistry and Molecular Biology, Georgetown University School of Medicine, Washington, DC, 20007, USA
SOURCE: Cancer Research (1998), 58(20), 4510-4514
CODEN: CNREA8; ISSN: 0008-5472
PUBLISHER: American Association for Cancer Research
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The antiangiogenic, tubulin-binding drug combretastatin A-4 exhibits a selective toxicity for proliferating endothelial cells in vitro and induces vascular shutdown in tumor models in vivo. The mechanism of combretastatin A-4 cytotoxicity has now been investigated with cultured proliferating human umbilical vein endothelial cells by exams. various markers of apoptosis. Incubation of cells with 0.1 mM combretastatin A-4 induced the conversion (first detected after 6 h) of the CPP32 proenzyme to active caspase-3, a cysteine protease that plays an important role in apoptosis in many cell types; the drug also increased caspase-3 activity. Another early event obsd. was the binding of annexin V to 50% of the cells 8 h after drug treatment. Internucleosomal DNA fragmentation, another hallmark of apoptosis, was detected in cells incubated with 0.1 mM combretastatin A-4 for 24 h. Staining with Hoechst 33258 revealed that *about 75% of cells exhibited a nuclear morphol. characteristic of* apoptosis after incubation with drug for 24 h. Incubation of cells for up to 8 h with combretastatin A-4 did not induce the release of lactate dehydrogenase or increase the uptake of propidium iodide, both indicators of membrane integrity. These results indicate that the selective cytotoxic effect of combretastatin A-4 is mediated by the induction of apoptosis rather than by necrosis and may provide an enhanced clin. strategy in cancer chemotherapy with this new agent.

IT **117048-59-6**, Combretastatin A-4
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(induction of apoptosis in proliferating human endothelial cells by the tumor-specific antiangiogenesis agent combretastatin A-4)

RN 117048-59-6 CAPLUS
CN Phenol, 2-methoxy-5-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



REFERENCE COUNT: 17 THERE ARE 17 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L24 ANSWER 105 OF 157 CAPLUS COPYRIGHT 2003 ACS (Continued)

L24 ANSWER 106 OF 157 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1998:612092 CAPLUS
DOCUMENT NUMBER: 129:245037
TITLE: Benzo[b]thiophene derivatives, analogs, and combretastatin nitrogen derivatives, useful as anti-mitotic agents which inhibit tubulin polymerization, and as antitumor agents
INVENTOR(S): Pinney, Kevin G.; Pettit, George R.; Mocharla, Vani P.; Del, Pilar Majia Maria; Shirali, Anupama
PATENT ASSIGNEE(S): Baylor University, USA; Arizona Disease Control Research Commission; Del Pilar Majia, Maria
SOURCE: PCT Int. Appl., 85 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9839323	A1	19980911	WO 1998-US4380	19980306
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, GW, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
US 5886025	A	19990323	US 1997-813018	19970306
AU 9866886	A1	19980922	AU 1998-66886	19980306
AU 732917	B2	20010503		
EP 984954	A1	20000315	EP 1998-908991	19980306
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
NZ 337866	A	20010629	NZ 1998-337866	19980306
JP 2001527533	T2	20011225	JP 1998-538834	19980306
MX 9908166	A	20000831	MX 1999-8166	19990906
US 6162930	A	20001219	US 1999-380429	19991203
US 2001034454	A1	20011025	US 2000-738394	20001215

PRIORITY APPLN. INFO.: US 1997-813018 A 19970306
WO 1998-US4380 W 19980306
US 1999-380429 A1 19991203

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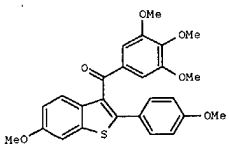
L24 ANSWER 106 OF 157 CAPLUS COPYRIGHT 2003 ACS (Continued)



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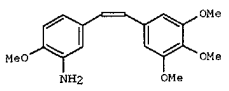


II

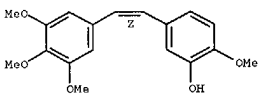
AB Methoxy- and ethoxy-substituted 3-aroyl-2-arylbenzo[b]thiophenes and benzo[b]thiophene analogs are described. The compds. are useful for inhibiting tubulin polymn., and thus for treating both tumors and infections with flagellated protozoa. Also described are certain diaryl ether benzo[b]thiophene derivs., as well as some analogs derived from dihydronaphthalene, which have proven particularly effective. Certain new benzofuran analogs are further described, as well as certain sulfur oxide benzo[b]thiophene analogs. Important compds. described herein also include the first nitrogen-contg. derivs. of combretastatin. These include nitro, amino and azido combretastatin derivs. For instance, acylation of 2-(4-methoxyphenyl)-6-methoxybenzo[b]thiophene by 3,4,5-trimethoxybenzoyl chloride and AlCl3 in CH2Cl2 gave 63% title compd. I. The IC50 of I for inhibiting tubulin polymn. in vitro was 1.5-2.5 .mu.M, while that for inhibiting growth of 6 human cancer cell lines was 0.049-0.48 .mu.g/mL. Against a different selection of 6 cancer cell lines, the amino combretastatin deriv. II gave even greater growth inhibitions, with IC50 values of 0.0013 .mu.g/mL or less.

IT **117048-59-6P**, Combretastatin
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of benzothiophenes and analogs as tubulin polymn. inhibitors and antitumor agents)

RN 117048-59-6 CAPLUS
CN Phenol, 2-methoxy-5-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

Double bond geometry as shown.

L24 ANSWER 106 OF 157 CAPLUS COPYRIGHT 2003 ACS (Continued)



REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

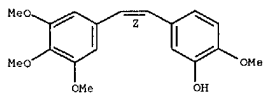
L24 ANSWER 107 OF 157 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1998:496731 CAPLUS
DOCUMENT NUMBER: 129:211245
TITLE: Antimitotic activity of diaryl compounds with structural features resembling combretastatin A-4
AUTHOR(S): Aleksandrzak, Krzysztof; McGown, Alan T.; Hadfield, John A.
CORPORATE SOURCE: Cancer Research Campaign Section Drug Development Imaging, Paterson Institute Cancer Research, Christie Hospital NHS Trust, Manchester, M20 4BX, UK
SOURCE: Anti-Cancer Drugs (1998), 9(6), 545-550
CODEN: ANTDEV; ISSN: 0959-4973
PUBLISHER: Lippincott-Raven Publishers
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Series of diaryl ethers, amines and amides have been synthesized and tested for antitumor activity. These diaryl compds. possess some of the structural features of combretastatin A-4 (a potent antimitotic agent). They were designed to discover whether transferring these structural motifs from stilbenes to heterosubstituted diaryl compds. would enhance their biochem. activities. Mol. modeling studies suggested that these diaryl compds. could adopt conformations similar to combretastatin A-4. However, although some agents were cytotoxic and others could interact with tubulin, none were as potent as combretastatin A-4.

IT **117048-59-6**, Combretastatin A-4
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(antimitotic activity of diaryl compds. with structural features resembling combretastatin A-4)

RN 117048-59-6 CAPLUS
CN Phenol, 2-methoxy-5-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

Double bond geometry as shown.

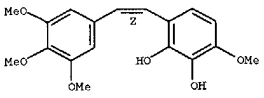


IT **109971-63-3**
RL: PRP (Properties)
(antimitotic activity of diaryl compds. with structural features resembling combretastatin A-4)

RN 109971-63-3 CAPLUS
CN 1,2-Benzenediol, 3-methoxy-6-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

Double bond geometry as shown.

L24 ANSWER 107 OF 157 CAPLUS COPYRIGHT 2003 ACS (Continued)



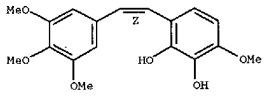
REFERENCE COUNT: 17 THERE ARE 17 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L24 ANSWER 108 OF 157 CAPLUS COPYRIGHT 2003 ACS (Continued)
of a nitrogen-contg. group. Among the compds. synthesized, those with an amino moiety in place of the phenolic OH of CA-4 showed potent antitubulin activity and cytotoxicity against murine Colon 26 adenocarcinoma in vitro. Some of the compds. which were potent in vitro were evaluated in the murine tumor model Colon 26 in vivo. Among these, I.cntdot.HCl (R1 = CN, R2 = NH2, R3 = OMe), and II.cntdot.HCl (R4 = R5 = H, R6 = OMe, Me) showed significant antitumor activity in the animal model, while CA-4 was ineffective. I.cntdot.HCl (R1 = CN, R2 = NH2, R3 = OMe), and II.cntdot.HCl (R4 = R5 = H, R6 = OMe) were further evaluated in two murine tumor models (Colon 38 and 3LL) and human xenografts HCT-15. These compds. showed potent antitumor activity comparable or superior to that of CDDP. The structure-activity relationships of this series of compds. are also discussed.

IT **109971-63-3DP**, Combretastatin A-1, analogs **117048-59-6DP**
, Combretastatin A-4, analogs
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(prepn. and antitumor structure-activity relationships of combretastatin analogs)

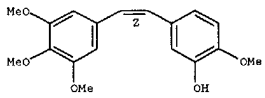
RN 109971-63-3 CAPLUS
CN 1,2-Benzenediol, 3-methoxy-6-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



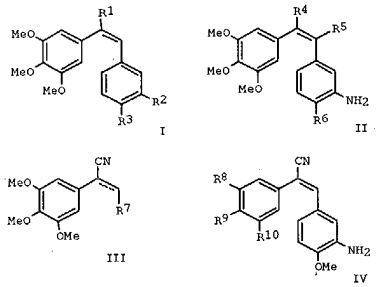
RN 117048-59-6 CAPLUS
CN Phenol, 2-methoxy-5-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



REFERENCE COUNT: 28 THERE ARE 28 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L24 ANSWER 108 OF 157 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1998:450903 CAPLUS
DOCUMENT NUMBER: 129:202788
TITLE: Novel Combretastatin Analogs Effective against Murine Solid Tumors: Design and Structure-Activity Relationships
AUTHOR(S): Ohsumi, Koji; Nakagawa, Ryusuke; Fukuda, Yumiko; Hatanaka, Toshihiro; Morinaga, Yoshihiro; Nihei, Yukio; Ohishi, Kazuo; Suga, Yasuyo; Akiyama, Yukio; Tsuji, Takashi
CORPORATE SOURCE: Central Research Laboratories, Ajinomoto Company Ltd., Kawasaki, 210 JAPAN, Japan
SOURCE: Journal of Medicinal Chemistry (1998), 41(16), 3022-3032
CODEN: JMCMAR; ISSN: 0022-2623
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
GI



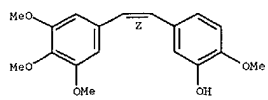
AB A series of combretastatin A-4 (CA-4) analogs, I (R1 = CH2OH, CH2NH2, NH2N+Me3I-, CHO, CN, R2 = H, R3 = OMe; R1 = CN, R2 = NO2, OH, NH2, R3 = OMe; R1 = CN, R2 = NH2, R3 = Me, Cl; R1 = CN, R2 = NHAc, R3 = OMe), II (R4 = H, R5 = CONH2, CN, H, R6 = OMe; R4 = CONH2, CN, R5 = H, R6 = OMe; R4 = R5 = H, R6 = Me, Cl), III (dashed line = double bond, R7 = C6H4OMe-4, C6H4OMe-4-NO2-3, C6H4OMe-4-NH2-3, C6H4Me-4-NH2-3, 2-methoxy-5-pyridyl; dashed line = single bond, R7 = C6H4OMe-4, C6H4OMe-4-NO2-3, C6H4OMe-4-NH2-3, 2-methoxy-5-pyridyl) and IV (R8 = R9 = R10 = H, OMe; R8 = R10 = H, R9 = OMe; R8 = R9 = OMe, R10 = H), were synthesized, and their cytotoxic effects against murine Colon 26 adenocarcinoma and inhibitory activity on tubulin polymn. were evaluated. Since CA-4 has limited aq. soly., the target compds. were designed to improve soly. by introduction

L24 ANSWER 109 OF 157 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1998:404526 CAPLUS
DOCUMENT NUMBER: 129:172497
TITLE: Magnetic resonance imaging and spectroscopy of combretastatin A4 prodrug-induced disruption of tumor perfusion and energetic status
AUTHOR(S): Beauregard, D. A.; Thelwall, P. E.; Chaplin, D. J.; Hill, S. A.; Adams, G. E.; Brindle, K. M.
CORPORATE SOURCE: Department of Biochemistry, University of Cambridge, Cambridge, CB2 1GA, UK
SOURCE: British Journal of Cancer (1998), 77(11), 1761-1767
CODEN: BJCAAI; ISSN: 0007-0920
PUBLISHER: Churchill Livingstone
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The effects of combretastatin A4 prodrug on perfusion and the levels of 31P metabolites in an implanted murine tumor were investigated for 3 h after drug treatment using NMR imaging (MRI) and spectroscopy (MRS). The area of regions of low signal intensity in spin-echo images of tumors increased slightly after treatment with the drug. These regions of low signal intensity corresponded to necrosis seen in histol. sections, whereas the expanding regions surrounding them corresponded to hemorrhage. Tumor perfusion was assessed before and 160 min after drug treatment using dynamic MRI measurements of gadolinium diethylenetriaminepentaacetate (Gd DTPA) uptake and washout. Perfusion decreased significantly in central regions of the tumor after treatment. This was attributed to disruption of the vasculature and was consistent with the hemorrhage seen in histol. sections. The mean apparent diffusion coeff. of water within the tumor did not change, indicating that there was no expansion of necrotic regions during the 3 h after drug treatment. Localized 31P-MRS showed that there was decline in cellular energy status in the tumor after treatment with the drug. The concns. of nucleoside triphosphates within the tumor fell, the inorg. phosphate concn. increased and there was a significant decrease in tumor pH for 80 min after drug treatment. The rapid, selective and extensive damage caused to these tumors by combretastatin A4 prodrug has highlighted the potential of the agent as a novel cancer chemotherapeutic agent. We have shown that the response of tumors to treatment with the drug may be monitored non-invasively using MRI and MRS expts. that are appropriate for use in a clin. setting.

IT **117048-59-6**, Combretastatin A4
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(magnetic resonance imaging and spectroscopy of combretastatin A4 prodrug-induced disruption of tumor perfusion and energetic status)

RN 117048-59-6 CAPLUS
CN Phenol, 2-methoxy-5-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



REFERENCE COUNT: 20 THERE ARE 20 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L24 ANSWER 109 OF 157 CAPLUS COPYRIGHT 2003 ACS (Continued)

L24 ANSWER 110 OF 157 CAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 1998:301433 CAPLUS
DOCUMENT NUMBER: 129:36213
TITLE: Antineoplastic agents. 389. New syntheses of the combretastatin A-4 prodrug
AUTHOR(S): Pettit, George R.; Rhodes, Monte R.
CORPORATE SOURCE: Cancer Research Institute and Department of Chemistry, Arizona State University, Tempe, AZ, 85287-2404, USA
SOURCE: Anti-Cancer Drug Design (1998), 13(3), 183-191
CODEN: ACDDEA; ISSN: 0266-9536
PUBLISHER: Oxford University Press
DOCUMENT TYPE: Journal
LANGUAGE: English
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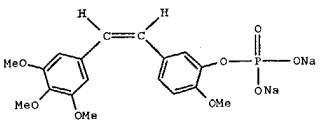


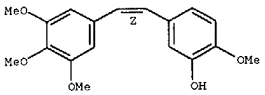
I

AB Combretastatin A-4 as the phosphate ester prodrug I is a potent antineoplastic and antiangiogenesis substance and is in advanced preclin. development. For the purpose of improving the phosphorylation synthetic sequence from combretastatin A-4, new routes were studied. The phosphorylation step is considerably improved using in situ-generated dibenzyl chlorophosphite. Cleavage of the benzyl esters employing a trimethylchlorosilane/NaI procedure, followed by treatment with Na methoxide, led to the water-sol. prodrug I in high yield.

IT **117048-59-6**
RL: RCT (Reactant); RACT (Reactant or reagent)
(prepn. of combretastatin A-4 prodrug)

RN 117048-59-6 CAPLUS
CN Phenol, 2-methoxy-5-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



REFERENCE COUNT: 37 THERE ARE 37 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L24 ANSWER 110 OF 157 CAPLUS COPYRIGHT 2003 ACS (Continued)

L24 ANSWER 111 OF 157 CAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 1998:253141 CAPLUS
DOCUMENT NUMBER: 128:230173
TITLE: Antineoplastic Agents. 379. Synthesis of Phenstatin Phosphate
AUTHOR(S): Pettit, George R.; Toki, Brian; Herald, Delbert L.; Verdier-Pinard, Pascal; Boyd, Michael R.; Hamel, Ernest; Pettit, Robin K.
CORPORATE SOURCE: Cancer Research Institute and Department of Chemistry, Arizona State University, Tempe, AZ, 85287-1604, USA
SOURCE: Journal of Medicinal Chemistry (1998), 41(10), 1688-1695
CODEN: JMCMAR; ISSN: 0022-2623
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
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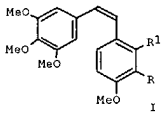
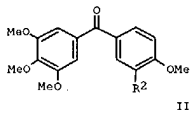


I



II

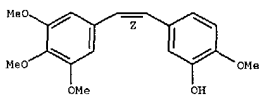
AB A structure-activity relationship (SAR) study of the South African willow tree (Combretum caffrum) antineoplastic constituent combretastatin A-4 (I; R = OH, R1 = H) directed at maintaining the (Z)-stilbene relationship of the olefin di-Ph substituents led to synthesis of a potent cancer cell growth inhibitor designated phenstatin (II; R2 = OH). Initially phenstatin silyl ether (II; R2 = OSiMe2CMe3) was unexpectedly obtained by Jacobsen oxidn. of combretastatin A-4 silyl ether (I; R = OSiMe2CMe2, R1 = H), and the parent phenstatin (II; R2 = OH) was later synthesized in quantity. Phenstatin was converted to the sodium phosphate prodrug [II; R2 = OP(O)(ONa)2] by a dibenzyl phosphite phosphorylation and subsequent hydrogenolysis sequence. Phenstatin (II; R2 = OH) inhibited growth of the pathogenic bacterium Neisseria gonorrhoeae and was a potent inhibitor of tubulin polymn. and the binding of colchicine to tubulin comparable to combretastatin A-4 (I; R = OH, R1 = H). Interestingly, the prodrugs were found to have reduced activity in these biochem. assays. While no significant tubulin activity was obsd. with the phosphorylated deriv. of combretastatin A-4 (I; R = OH, R1 = H), phosphate II [R2 = OP(O)(ONa)2] retained detectable inhibitory effects in both assays.

IT **117048-59-6DP**, Combretastatin A-4, analogs and prodrugs
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(structure-activity relationship of the antineoplastic agent combretastatin A-4)

RN 117048-59-6 CAPLUS
CN Phenol, 2-methoxy-5-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

Double bond geometry as shown.

L24 ANSWER 111 OF 157 CAPLUS COPYRIGHT 2003 ACS (Continued)



L24 ANSWER 112 OF 157 CAPLUS COPYRIGHT 2003 ACS

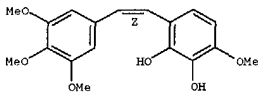
ACCESSION NUMBER: 1998:232843 CAPLUS
DOCUMENT NUMBER: 128:316915
TITLE: Using a canonical matching to measure the similarity between molecules: the taxol and the combretastatin A1 case
AUTHOR(S): Sello, Guido; Termini, Manuela
CORPORATE SOURCE: Department of Organic and Industrial Chemistry, University of Milano, Milan, Italy
SOURCE: Advances in Molecular Similarity (1996), 1, 243-266
CODEN: AMOSFB
PUBLISHER: JAI Press
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The incomplete understanding of tumor proliferation and the structural complexity of the few natural antitumor agents are impediments to the prodn. of effective synthetic drugs. Polyhydroxyphenol derivs. with stilbenic skeleton, such as some combretastatin A1 derivs., proved to be promising as potential antitumor agents. The possibility of modeling structure and biol. activity relationships could allow us to find new drugs to be synthesized more easily and with controlled pharmacol. properties, such as activity and selectivity, thus giving great benefits. Knowing the structure and the properties of one of the few antitumor drugs currently available (taxol) and having at our disposal an anal. method to detect similarities, we started a conformational study of the similarity between taxol and some combretastatin A1 derivs. The aim was to check the possibility of these simple compds. to substitute taxol for its biol. activity. The results obtained have been compared to those from a modeling program (CHEMX) to test and confirm the correctness of our methodol.

IT **109971-63-3**, Combretastatin A1
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(using a canonical matching to measure the similarity between mols. in antitumor drug design)

RN 109971-63-3 CAPLUS
CN 1,2-Benzenediol, 3-methoxy-6-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

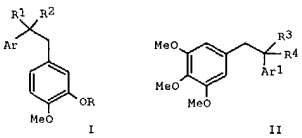
Double bond geometry as shown.



REFERENCE COUNT: 10 THERE ARE 10 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

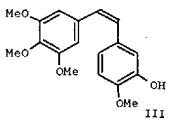
L24 ANSWER 113 OF 157 CAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 1998:222502 CAPLUS
DOCUMENT NUMBER: 128:294632
TITLE: Synthesis and antineoplastic activity of combretastatin analogs: heterocombretastatins
AUTHOR(S): Medarde, Manuel; Ramos, Angel; Caballero, Esther; Pelaez-Lamamie de Clairac, Rafael; Lopez, Jose Luis; Gravalos, Dolores Garcia; San Feliciano, Arturo
CORPORATE SOURCE: Departamento de Quimica Farmaceutica, Facultad de Farmacia, Salamanca, E-37007, Spain
SOURCE: European Journal of Medicinal Chemistry (1998), 33(1), 71-77
CODEN: EJMCA5; ISSN: 0223-5234
PUBLISHER: Editions Scientifiques et Medicales Elsevier
DOCUMENT TYPE: Journal
LANGUAGE: English
GI



I

II



III

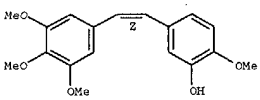
AB Furan and indole analogs I (Ar = 2-furyl, R = H, R1R2 = O; Ar = 3-furyl, 5-methyl-2-furyl, 1-methylindol-3-yl, R = R1 = R2 = H; Ar = 2-furyl, 3-furyl, 5-methyl-2-furyl, 1-methylindol-3-yl, R = CH2Ph, R1R2 = SCH2CH2CH2S) and II (Ar1 = 2-furyl, 3-furyl, 5-methyl-2-furyl, 1-methylindol-3-yl, R3 = R4 = H; Ar1 = 2-furyl, 3-furyl, 5-methyl-2-furyl, 1-methylindol-3-yl, R3R4 = O, SCH2CH2CH2S; Ar1 = 2-furyl, 3-furyl, R3 = OH, R4 = H) of combretastatin A-4 (III) were prepd. and assayed for antineoplastic activity. II (Ar1 = 1-methylindol-3-yl, R1R2 = O) showed the best activity [IC50 = 0.6 .mu.M vs. P-388, A-549, HT-29 cells; IC50 = 0.3 vs. MEL-28 cells].

IT **117048-59-6DP**, Combretastatin A-4, furan and indole analogs
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(synthesis and antineoplastic activity of furan and indole analogs of combretastatin)

RN 117048-59-6 CAPLUS
CN Phenol, 2-methoxy-5-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA

L24 ANSWER 113 OF 157 CAPLUS COPYRIGHT 2003 ACS (Continued)
INDEX NAME)

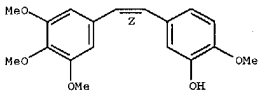
Double bond geometry as shown.



REFERENCE COUNT: 25 THERE ARE 25 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L24 ANSWER 114 OF 157 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1998:212786 CAPLUS
DOCUMENT NUMBER: 128:292670
TITLE: Microtubule depolymerization in Uromyces appendiculatus by three new antineoplastic drugs: combretastatin A-4, dolastatin 10 and halichondrin B
AUTHOR(S): Roberson, Robert W.; Tucker, Bruce; Pettit, George R.
CORPORATE SOURCE: Department of Botany, Arizona State University, Tempe, AZ, 85287-1601, USA
SOURCE: Mycological Research (1998), 102(3), 378-382
CODEN: MYCRER; ISSN: 0953-7562
PUBLISHER: Cambridge University Press
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Three new antineoplastic natural products, combretastatin A-4, dolastatin 10 and halichondrin B, have been evaluated for their antimicrotubule activity in Uromyces appendiculatus urediniospore germlings using indirect immunofluorescence microscopy. In control germlings microtubules were abundant and mostly oriented parallel to the longitudinal axis of the cell. The microtubule cytoskeleton of germlings treated with 1.3 .times. 10-5 M (10 .mu.g ml-1) dolastatin 10 and 4.5 .times. 10-5 M (50 .mu.g ml-1) halichondrin B disrupted the microtubule cytoskeleton resulting in the near elimination of microtubule-assocd. fluorescence. Combretastatin A-4 was less effective, requiring a concn. of 3.2 .times. 10-3 M (1.0 mg ml-1) to disrupt the microtubule cytoskeleton. These EDs are consistent with previously examd. antimicrotubule agents (e.g. nocodazole, griseofulvin, vincristine sulfate, and demecolcine).
IT **117048-59-6**, Combretastatin A-4
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(microtubule depolymn. in Uromyces appendiculatus by three new antineoplastic drugs: combretastatin A-4, dolastatin 10 and halichondrin B)
RN 117048-59-6 CAPLUS
CN Phenol, 2-methoxy-5-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

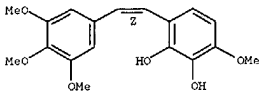
Double bond geometry as shown.



REFERENCE COUNT: 17 THERE ARE 17 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L24 ANSWER 115 OF 157 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1997:720292 CAPLUS
DOCUMENT NUMBER: 127:302918
TITLE: Isolation, Synthesis, and Antiplatelet Aggregation Activity of Resveratrol 3-O-.beta.-D-glucopyranoside and Related Compounds
AUTHOR(S): Orsini, Fulvia; Verotta, Luisella; Aburjai, Talal; Rogers, Colin B.
CORPORATE SOURCE: Centro di Studio per le Sostanze Organiche Naturali, CNR, Milan, 20133, Italy
SOURCE: Journal of Natural Products (1997), 60(11), 1082-1087
CODEN: JNPRDF; ISSN: 0163-3864
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Resveratrol 3-O-.beta.-D-glucopyranoside (I) has been isolated from the seeds of Erythrophleum lasianthum (Caesalpinioidae, Leguminosae), a South African plant used in traditional medicine, and has shown antiplatelet aggregation activity. The synthesis of I, related hydroxystilbenes, and their glucosides has been undertaken to provide larger quantities, for further biol. evaluation, and has been accomplished via Wittig reactions followed by glucosylation under phase transfer catalysis.
IT **109971-63-3 117048-59-6**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(resveratrol O-.beta.-D-glucopyranoside isolation, synthesis, and antiplatelet aggregation activity of resveratrol 3-O-.beta.-D-glucopyranoside and related compds.)
RN 109971-63-3 CAPLUS
CN 1,2-Benzenediol, 3-methoxy-6-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

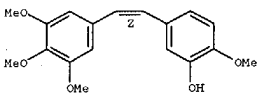
Double bond geometry as shown.



RN 117048-59-6 CAPLUS
CN Phenol, 2-methoxy-5-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

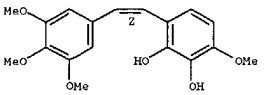
Double bond geometry as shown.

L24 ANSWER 115 OF 157 CAPLUS COPYRIGHT 2003 ACS (Continued)



L24 ANSWER 116 OF 157 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1997:452036 CAPLUS
DOCUMENT NUMBER: 127:121925
TITLE: Synthesis of biologically active polyphenolic glycosides (combretastatin and resveratrol series)
AUTHOR(S): Orsini, Fulvia; Pelizzoni, Francesca; Bellini, Barbara; Miglierini, Giuliana
CORPORATE SOURCE: Dipartimento di Chimica Organica e Industriale, Centro di Studio per le Sostanze Organiche Naturali del CNR, Milan, 20133, Italy
SOURCE: Carbohydrate Research (1997), 301(3-4), 95-109
CODEN: CRBRAT; ISSN: 0008-6215
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal
LANGUAGE: English
AB (E)-3-(.beta.-D-Glucopyranosyloxy)-4',5-dihydroxystilbene (resveratrol 3-.beta.-D-glucoside, piceid), (Z)-2',3'-dihydroxy-3,4,4'5-tetramethoxystilbene (combretastatin A-1), (Z)-3'-hydroxy-3,4,4'5-tetramethoxystilbene (combretastatin A-4), (Z)-2'-hydroxy-3,4,4',5-tetramethoxystilbene (combretastatin iso-A-4), .alpha.,.beta.-dihydro-2',3'-dihydroxy-3,4,4',5-tetramethoxystilbene (combretastatin B-1), the corresponding glucosides, and related compds. have been synthesized via Wittig reactions followed by glucosylation under phase-transfer catalysis. Most of the compds. synthesized have been tested with respect to biol. activity (cytostatic, cytotoxic, antimitotic, neurotoxic, antiplatelet aggregation activity).
IT **109971-63-3P 109984-84-1P 117048-59-6P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); RCT (Reactant); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent)
(prepn. of biol. active polyphenolic glycosides)
RN 109971-63-3 CAPLUS
CN 1,2-Benzenediol, 3-methoxy-6-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

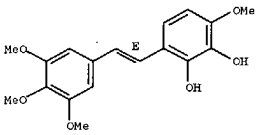
Double bond geometry as shown.



RN 109984-84-1 CAPLUS
CN 1,2-Benzenediol, 3-methoxy-6-[(1E)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

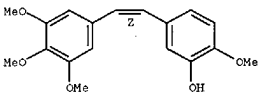
Double bond geometry as shown.

L24 ANSWER 116 OF 157 CAPLUS COPYRIGHT 2003 ACS (Continued)



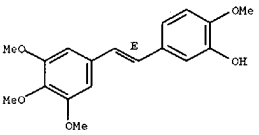
RN 117048-59-6 CAPLUS
CN Phenol, 2-methoxy-5-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



IT **117048-62-1P 156085-79-9P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(prepn. of biol. active polyphenolic glycosides)
RN 117048-62-1 CAPLUS
CN Phenol, 2-methoxy-5-[(1E)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

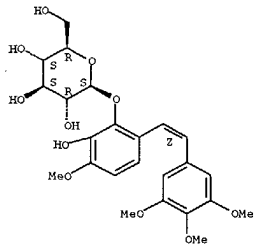
Double bond geometry as shown.



RN 156085-79-9 CAPLUS
CN .beta.-D-Glucopyranoside, 2-hydroxy-3-methoxy-6-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]phenyl (9CI) (CA INDEX NAME)

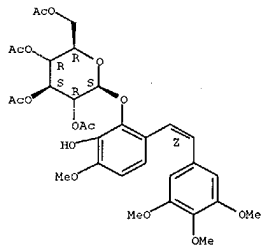
Absolute stereochemistry. Rotation (+).

L24 ANSWER 116 OF 157 CAPLUS COPYRIGHT 2003 ACS (Continued)
Double bond geometry as shown.



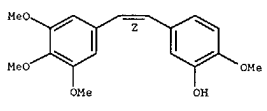
IT **192711-05-0P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(prepn. of biol. active polyphenolic glycosides)
RN 192711-05-0 CAPLUS
CN .beta.-D-Glucopyranoside, 2-hydroxy-3-methoxy-6-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]phenyl, 2,3,4,6-tetraacetate (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).
Double bond geometry as shown.



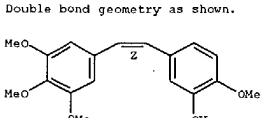
L24 ANSWER 117 OF 157 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1997:335437 CAPLUS
DOCUMENT NUMBER: 127:60262
TITLE: Combretastatin A-4, an agent that displays potent and selective toxicity toward tumor vasculature
AUTHOR(S): Dark, Graham G.; Hill, Sally A.; Prise, Vivien E.; Tozer, Gillian M.; Pettit, George R.; Chaplin, Dai J.
CORPORATE SOURCE: Tumour Microcirculation Group, Gray Laboratory Cancer Research Trust, Mount Vernon Hospital, Northwood, HA6 2JR, UK
SOURCE: Cancer Research (1997), 57(10), 1829-1834
CODEN: CNREA8; ISSN: 0008-5472
PUBLISHER: American Association for Cancer Research
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Selective induction of vascular damage within tumors represents an emerging approach to cancer treatment. Histol. studies have shown that several tubulin-binding agents can induce vascular damage within tumors but only at doses approximating the max. tolerated dose, which has limited their clin. applicability. In this study, we show that the combretastatin A-4 prodrug induces vascular shutdown within tumors at doses less than one-tenth of the max. tolerated dose. In vitro studies indicate that a short drug exposure results in profound long-term antiproliferative/cytotoxic effects against proliferating endothelial cells but not cells that are quiescent prior to and during drug exposure. Vascular shutdown, within exptl. and human breast cancer models in vivo following systemic drug administration, was demonstrated with a redn. in functional vascular vol. of 93% at 6 h following drug administration and persisted over the next 12 h, with corresponding histol. consistent with hemorrhagic necrosis resulting from vascular damage. The actions against tumor vasculature and the broad therapeutic window demonstrate the clin. potential of these drugs and warrant further study to elucidate the mechanisms responsible for the antivascular effects of combretastatin A-4.
IT **117048-59-6**, Combretastatin A-4
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(combretastatin A-4 in toxicity toward tumor vasculature)
RN 117048-59-6 CAPLUS
CN Phenol, 2-methoxy-5-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



L24 ANSWER 118 OF 157 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1997:328692 CAPLUS
DOCUMENT NUMBER: 127:28629
TITLE: Synthesis and biological evaluation of 1,1-dichloro-2,3-diarylcyclopropanes as antitubulin and anti-breast cancer agents
AUTHOR(S): Jonnalagadda, Sastry S.; Ter Haar, Ernst; Hamel, Ernest; Lin, Chii M.; Magarian, Robert A.; Day, Billy W.
CORPORATE SOURCE: Department of Environmental and Occupational Health, University of Pittsburgh, Pittsburgh, PA, 15238, USA
SOURCE: Bioorganic & Medicinal Chemistry (1997), 5(4), 715-722
CODEN: BMECEP; ISSN: 0968-0896
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Z-1,1-Dichloro-2,3-diphenylcyclopropane (1) is an effective anti-breast cancer agent in rodents and in cell culture. We recently detd. that 1 inhibits tubulin assembly in vitro and causes microtubule loss in breast cancer cells, leading to accumulation in the G2/M portion of the cell cycle. Aryl ring-halogenated, methoxylated and benzyloxylated derivs. of 1, as well as its E-isomer and the dichlorocyclopropyl deriv. of diethylstilbesrol (DES), were synthesized and tested for their ability to inhibit the assembly of tubulin into microtubules. Including 1, 17 cyclopropyl compds. were tested. One (Z-1,1-dichloro-2-(4-methoxyphenyl)-3-phenylcyclopropane) was found to be more active than 1. In addn., E-1,1-dichlorocyclopropylDES was more potent than DES. The E-isomer of 1 was inactive. The cytostatic activities of the compds. against MCF-7 and MDA-MB231 human breast cancer cells, and their abilities to perturb microtubules in MCF-7 cells were also evaluated. Z-Dichloro-2-(4-fluorophenyl)-3-phenylcyclopropane, Z-1,1-dichloro-2-(4-fluorophenyl)-3-(4-methoxyphenyl)cyclopropane, and Z-1,1-dichloro-2-(4-methoxyphenyl)-3-phenylcyclopropane were more potent than 1 against the breast cancer cells.
IT **117048-59-6**, Combretastatin A-4
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(synthesis and biol. evaluation of 1,1-dichloro-2,3-diarylcyclopropanes as antitubulin and anti-breast cancer agents)
RN 117048-59-6 CAPLUS
CN Phenol, 2-methoxy-5-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



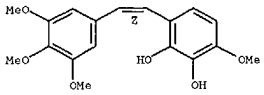
L24 ANSWER 119 OF 157 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1997:198361 CAPLUS
DOCUMENT NUMBER: 126:258604
TITLE: Effects of novel and conventional anti-cancer agents on human endothelial permeability: influence of tumor secreted factors
AUTHOR(S): Watts, Margaret E.; Woodcock, Michael; Arnold, Stephanie; Chaplin, David J.
CORPORATE SOURCE: Tumor Microcirculation Group, Gray Lab. Cancer Res. Trust, Middlesex, HA6 2JR, UK
SOURCE: Anticancer Research (1997), 17(1A), 71-75
CODEN: ANTRD4; ISSN: 0250-7005
PUBLISHER: Anticancer Research
DOCUMENT TYPE: Journal
LANGUAGE: English

AB A no. of anti-cancer agents have been implicated in vascular toxicity. The effects have been attributed to direct drug toxicity towards endothelium. Little attention has been focused on the interaction between anticancer drugs, endothelial cells and tumor secreted factors. It is well known that tumors can secrete factors such as vascular permeability factor which do affect endothelial cells and could alter their response to the vascular effects of anticancer drugs. In the present study, we have exaind., in vitro, the direct effects of vinblastine (VBL), 5-fluorouracil (5-FU), melphalan (L-PAM) and the novel tubulin inhibitor combretastatin A-1 (CBS) on endothelial permeability under normal and tumor simulated conditions. Monolayers of human umbilical vein endothelial cells (HUVEC) grown on membrane filters were incubated by the human melanoma cell line, RPMI-7951 (TCM). VBL caused rapid increase in permeability during the first 20 mins, which was maintained for the duration of the expt. (120 mins). The effect was not altered by TCM or restored to control levels when VBL was replaced by drug-free medium. Similarly, CBS caused a rapid increase in permeability; however, in contrast to VBL, this increase was enhanced by TCM. The changes induced by VBL and CBS were accompanied by contraction of the endothelial F-actin cytoskeleton. Neither L-PAM nor 5-FU altered the permeability of HUVEC monolayers. This study demonstrates that certain anti-cancer agents have a direct effect on endothelial cells, leading to an increase in the permeability of endothelial monolayers. Both VBL and CBS have vascular components in their mode of action which may lead to vascular collapse and tumor necrosis.

IT **109971-63-3**, Combretastatin A-1
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(novel and conventional antitumor drug effect on human endothelial permeability: influence of tumor secreted factors)
RN 109971-63-3 CAPLUS
CN 1,2-Benzenediol, 3-methoxy-6-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

Double bond geometry as shown.

L24 ANSWER 119 OF 157 CAPLUS COPYRIGHT 2003 ACS (Continued)

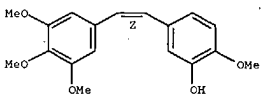


L24 ANSWER 120 OF 157 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1996:743457 CAPLUS
DOCUMENT NUMBER: 126:89204
TITLE: Ethynylation of aryl halides by a modified Suzuki reaction. Application to the syntheses of combretastatin A-4, A-5, and lunularic acid
AUTHOR(S): Fuerstner, Alois; Nikolakis, Katharina
CORPORATE SOURCE: Max-Planck-Institut Kohlenforschung, Muelheim an der Ruhr, D-45470, Germany
SOURCE: Liebigs Annalen (1996), (12), 2107-2113
CODEN: LANAEM; ISSN: 0947-3440
PUBLISHER: VCH
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 126:89204

AB On treatment with B(OMe)3, NaCCH undergoes a Pd-catalyzed cross coupling with functionalized aryl halides or triflates in reasonable to good yields. The ethynylarenes thus obtained serve as building blocks for the formation of the highly effective tubulin polymn. inhibitors combretastatin A-4 and A-5 as well as for the synthesis of the plant-growth regulator lunularic acid.

IT **117048-59-6P**, Combretastatin A-4
RL: SPN (Synthetic preparation); PREP (Preparation)
(syntheses of combretastatin A-4, A-5, and lunularic acid via ethynylation of aryl halides by modified Suzuki reaction)
RN 117048-59-6 CAPLUS
CN Phenol, 2-methoxy-5-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

Double bond geometry as shown.

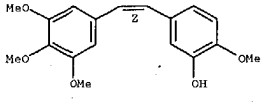


L24 ANSWER 121 OF 157 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1996:714628 CAPLUS
DOCUMENT NUMBER: 126:628
TITLE: Antitumor activity of combretastatin-A4 phosphate, a natural product tubulin inhibitor
AUTHOR(S): Dorr, Robert T.; Dvorakova, Katerina; Snead, Kristi; Alberts, David S.; Salmon, Sydney E.; Pettit, G. Robert
CORPORATE SOURCE: College Medicine, University Arizona, Tucson, AZ, USA
SOURCE: Investigational New Drugs (1996), 14(2), 131-137
CODEN: INNDDK; ISSN: 0167-6997
PUBLISHER: Kluwer
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The tubulin-binding natural product combretastatin A-4 (CA-4) was tested for antitumor activity against fresh human tumors in vitro and 2 mouse tumors, both in vitro and in vivo. In colony forming assays using 10% fetal bovine serum, CA-4 was inhibitory in 27/40 human ovary cancers with a mean IC50 of 3.18 .mu.g/mL for a 1-h exposure (specimens) and 0.27 .mu.g/mL for a continuous exposure to CA-4 for 11-14 days (specimens). Murine B-16 melanoma and P-388 leukemia were also highly sensitive to CA-4 in vitro with an identical IC50 value of 0.0007 .mu.g/mL for continuous drug exposure for 8 days. Comparable in vitro cell culture studies performed in serum concns. higher than 10%, revealed a significant loss of cytotoxic potency. Using the same reversed-phase HPLC technique as developed for paclitaxel, CA-4 was shown to bind to serum proteins (.gtoreq. 30,000 mw) > 99% and to albumin approx. 70%. CA-4 was only marginally active (25% increased lifespan) in DBA/2 mice bearing P-388 leukemia who were given doses of 100 mg/kg IP on either days, 1, 5 and 9 (by Wilcoxon anal.) or on consecutive days 1-9 (compared to control). A higher IP dose of 150 mg/kg on days 1, 5 and 9 did not delay s.c. B-16 melanoma tumor growth in C57/B1 mice. These findings demonstrate a substantial loss of antitumor efficacy for CA-4 in physiol. serum concns. in vitro. No consistent antitumor activity was obsd. in two murine tumor models in vivo.

IT **117048-59-6**, Combretastatin-A4
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(antitumor activity of combretastatin-A4 in human tumor cells and in mice)
RN 117048-59-6 CAPLUS
CN Phenol, 2-methoxy-5-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

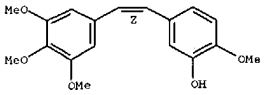
Double bond geometry as shown.



L24 ANSWER 122 OF 157 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1996:701793 CAPLUS
DOCUMENT NUMBER: 126:69728
TITLE: Computational and molecular modeling evaluation of the structural basis for tubulin polymerization inhibition by colchicine site agents
AUTHOR(S): ter Haar, Ernst; Rosenkranz, Herbert S.; Hamel, Ernest; Day, Billy W.
CORPORATE SOURCE: Dep. Environmental and Occupational Health, Univ. Pittsburgh Cancer Inst., Pittsburgh, PA, 15238, USA
SOURCE: Bioorganic & Medicinal Chemistry (1996), 4(10), 1659-1671
CODEN: BMECEP; ISSN: 0968-0896
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The computer-automated structure evaluation programs MultiCASE and CASE were used to perform a quant. structure-activity relationship study on tubulin polymn. inhibitors. A learning set of 536 chems. (202 active, 27 marginal, and 307 inactive), built using IC50 values for inhibition of tubulin polymn. or mitosis from this and previous studies, was used for artificial intelligence self-teaching. The algorithms successfully predicted the activity of agents in the learning set with >90% accuracy. Seventeen MultiCASE and 12 CASE (mostly included in the MultiCASE set) biophores (substructures significantly correlated with activity) were identified with a probability >0.95. Here the authors present the biophores of podophyllotoxins, colchicinoids, and certain combretastatins, each examd. for structure-activity relationships. For the podophyllotoxins and colchicinoids in the learning set, the correlations between obsd. and predicted potencies were >0.85. The algorithms recognized the importance of several known site, electronic, and steric effects in the 2 classes. A predictive QSAR (R2 = 0.98) was developed for combretastatin A-2 and dihydrocombretastatin analogs. The MultiCASE/CASE analyses were used in combination with mol. models to study relative orientations of colchicine, podophyllotoxin, combretastatin A-4, and steganacin at the colchicine site. This resulted in a new hypothesis, consistent with extensive published exptl. data, in which the C-ring and part of the B-ring of colchicine overlap with the A- and B-rings of podophyllotoxin. Consequently, the trimethoxyphenyl rings of colchicine and podophyllotoxin occupied different regions of space, each pointing out from a hydrophobic core occupied by the overlapping biophores. The mol. model of the highly potent combretastatin A-4 could fit into the model binding site in .gtoreq.3 different ways. The developed QSARs were used to identify the potent microtubule stabilizer discodermolide. Its identification, in concert with recently reported findings, suggest potential overlap in the colchicine and paclitaxel binding sites on tubulin.
IT **117048-59-6**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)
(computational and mol. modeling evaluation of structural basis for tubulin polymn. inhibition by colchicine site agents)
RN 117048-59-6 CAPLUS
CN Phenol, 2-methoxy-5-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

Double bond geometry as shown.

L24 ANSWER 122 OF 157 CAPLUS COPYRIGHT 2003 ACS (Continued)

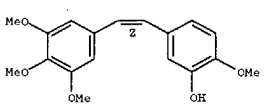


L24 ANSWER 123 OF 157 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1996:616598 CAPLUS
DOCUMENT NUMBER: 125:309027
TITLE: Combretastatin A-4 prodrug
INVENTOR(S): Pettit, George R.
PATENT ASSIGNEE(S): Arizona State University, USA
SOURCE: U.S., 7 pp.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 5561122	A	19961001	US 1994-363406	19941222

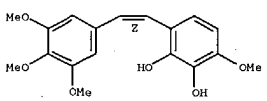
PRIORITY APPLN. INFO.: US 1994-363406 19941222
AB Disclosed herein are combretastatin A4 prodrugs with improved water soly. and stability, for the treatment of one or more neoplastic diseases by means of chemotherapy. Disodium combretastatin A4 3-O-phosphate (I) was prepd. and combretastatin A4 and I demonstrated similar in vitro activity levels in the NCI 60 cell line panel. Formulations contg. the prodrugs are provided.
IT **117048-59-6**, Combretastatin A4
RL: RCT (Reactant); RACT (Reactant or reagent)
(combretastatin A4 prodrugs and compns. contg. them)
RN 117048-59-6 CAPLUS
CN Phenol, 2-methoxy-5-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



L24 ANSWER 124 OF 157 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1996:492720 CAPLUS
DOCUMENT NUMBER: 125:185098
TITLE: Antivascular approaches to solid tumor therapy: Evaluation of tubulin binding agents
AUTHOR(S): Chaplin, DJ; Pettit, GR; Parkins, CS; Hill, SA
CORPORATE SOURCE: Gray Laboratory Cancer Research Trust, Mount Vernon Hospital, Northwood/Middlesex, HA6 2JR, USA
SOURCE: British Journal of Cancer, Supplement (1996), 74(27), S86-S88
CODEN: BJCSB5; ISSN: 0306-9443
PUBLISHER: Stockton
DOCUMENT TYPE: Journal
LANGUAGE: English
AB We have assessed the vascular effects of vinblastine and four other tubulin binding agents (dolastatin 10, dolastatin 15, combretastatin A1 and combretastatin A4), which are awaiting clin. evaluation. All five agents induce a redn. in tumor blood flow as measured by uptake of RbCl 24 h post drug administration. The degree of redn. ranged from 50% with combretastatin A1 to 90% with dolastatin 10. These redns. were similar to that seen with flavone acetic acid (FAA) and indicate that antivascular effects are a common feature of tubulin binding agents. We subsequently evaluated whether the blood flow redns., induced by FAA and vinblastine, could be used to enhance the activity of the bioreductive drug tirapazamine. Since the kinetics and extent of blood flow redns. induced by the agents is comparable, similar therapeutic response was expected. Potentiation was only evident with FAA, indicating that this effect is not directly related to killing of hypoxic tumor cells induced as a consequence of blood flow redn.
IT **109971-63-3**, Combretastatin A1 **117048-59-6**, Combretastatin A4
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(effect of tubulin binding agents and flavone acetic acid on tumor blood flow and tumor growth)
RN 109971-63-3 CAPLUS
CN 1,2-Benzenediol, 3-methoxy-6-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

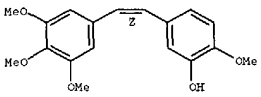
Double bond geometry as shown.



RN 117048-59-6 CAPLUS
CN Phenol, 2-methoxy-5-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

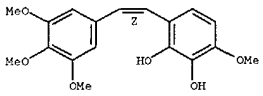
Double bond geometry as shown.

L24 ANSWER 124 OF 157 CAPLUS COPYRIGHT 2003 ACS (Continued)



L24 ANSWER 125 OF 157 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1996:258929 CAPLUS
DOCUMENT NUMBER: 125:25810
TITLE: New in vitro screening model for the discovery of antileukemic anticancer agents
AUTHOR(S): Valeriote, Frederick; Corbett, Thomas; Edelstein, Mark; Baker, Laurence
CORPORATE SOURCE: Harper-Grace Hospitals, Wayne State University, Detroit, MI, 48201, USA
SOURCE: Cancer Investigation (1996), 14(2), 124-41
CODEN: CINVD7; ISSN: 0735-7907
PUBLISHER: Dekker
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The authors describe the in vitro prescreen they have developed and are employing to select for new compds. active against human myelogenous leukemia and they present data from the in vitro screen together with parallel in vivo results. Three sets of compds. were tested: std. clin. employed anticancer agents, a set of purified natural products obtained from the NCI, and a no. of org. synthetic compds. obtained from the Sterling Research Corporation. The data provide a strong affirmation of the screening model to select for agents with in vivo activity.
IT **109971-63-3**, Combretastatin A-1
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(new in vitro screening model for discovery of antileukemic anticancer agents)
RN 109971-63-3 CAPLUS
CN 1,2-Benzenediol, 3-methoxy-6-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



L24 ANSWER 126 OF 157 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1996:108637 CAPLUS
DOCUMENT NUMBER: 124:260682
TITLE: Synthesis of water-soluble prodrugs of the cytotoxic agent combretastatin A4
AUTHOR(S): Bedford, Simon B.; Quarterman, Charmaine P.; Rathbone, Daniel L.; Slack, John A.; Griffin, Roger J.; Stevens, Malcolm F. G.
CORPORATE SOURCE: Aston Molecules Ltd., Birmingham, B7 4EJ, UK
SOURCE: Bioorganic & Medicinal Chemistry Letters (1996), 6(2), 157-60
CODEN: BMCLE8; ISSN: 0960-894X
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal
LANGUAGE: English
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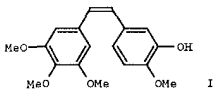
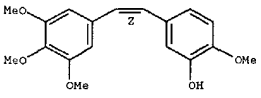


I

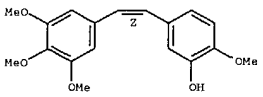
AB Water-sol. phosphate and glycine carbamate prodrugs of the cytotoxic agent Combretastatin A4 (I) have been prepd. The phosphate prodrug was degraded slowly in plasma at 37.degree.C. The degrdn. was accelerated by the addn. of alk. phosphatase.
IT **117048-59-6P**, Combretastatin A4
RL: SPN (Synthetic preparation); PREP (Preparation)
(synthesis of water-sol. prodrugs of the cytotoxic agent combretastatin A4)
RN 117048-59-6 CAPLUS
CN Phenol, 2-methoxy-5-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



L24 ANSWER 127 OF 157 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1995:923441 CAPLUS
DOCUMENT NUMBER: 124:20907
TITLE: Inhibition of [3H]mebendazole binding to tubulin by structurally diverse microtubule inhibitors which interact at the colchicine binding site
AUTHOR(S): Russell, Greogry J.; Lacey, Ernest
CORPORATE SOURCE: Dep. of Veterinary Pathology, Univ. of Sydney, 2006, Australia
SOURCE: Biochemistry and Molecular Biology International (1995), 35(6), 1153-9
CODEN: BMBIES; ISSN: 1039-9712
PUBLISHER: Academic
DOCUMENT TYPE: Journal
LANGUAGE: English
AB A rapid and convenient radioligand assay was used to characterize the interaction of several structurally diverse microtubule inhibitors with the colchicine binding domain of tubulin. Values detd. for the inhibition of [3H]mebendazole binding to tubulin by colchicine, combretastatin A4, NSC 181928, NSC 321567, podophyllotoxin and tubulozole-C provided an independent measure of the relative potency of these compds. This methodol. has several advantages over the inhibition of [3H]colchicine binding as a technique for investigating the mol. mechanisms involved in detg. tubulin-ligand interactions.
IT **117048-59-6**, Combretastatin A4
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(inhibition of [3H]mebendazole binding to tubulin by structurally diverse microtubule inhibitors which interact at the colchicine binding site)
RN 117048-59-6 CAPLUS
CN Phenol, 2-methoxy-5-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



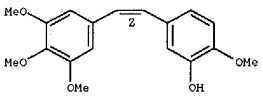
L24 ANSWER 128 OF 157 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1995:846307 CAPLUS
DOCUMENT NUMBER: 123:305988
TITLE: Characterization of the interaction of the marine cyanobacterial natural product curacin A with the colchicine site of tubulin and initial structure-activity studies with analogs
AUTHOR(S): Blokhin, Andrei V.; Yoo, Hye-Dong; Geralds, Robin S.; Nagle, Dale G.; Gerwick, William H.; Hamel, Ernest
CORPORATE SOURCE: Lab. Mol. Pharmacology, Developmental Therapeutics Program, Natinoal Cancer Institute, National Institutes Helath, Bethesda, MD, 20892, USA
SOURCE: Molecular Pharmacology (1995), 48(3), 523-31
CODEN: MOPMA3; ISSN: 0026-895X
PUBLISHER: Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Curacin A, the major lipid constituent of a strain of the marine cyanobacterium Lyngbya majuscula obtained off the coast of Curacao, is a potent antimitotic agent that we have previously shown to inhibit microtubule assembly and colchicine binding to tubulin. In the present study, we report that curacin A probably binds in the colchicine site because it competitively inhibits the binding of [3H]colchicine to tubulin with an apparent Ki value of 0.6 .mu.M and stimulates tubulin-dependent GTP hydrolysis, as do most other colchicine-site agents. The binding of curacin A to tubulin resembled the binding reactions of combretastatin A-4 and podophyllotoxin in contrast to that of colchicine in that it occurred as extensively on ice as at higher temps. However, once bound, the dissocn. rate of curacin A from tubulin was very slow, more closely resembling that obsd. with colchicinoids (thiocolchicine was the drug examd.) than the faster dissocn. that occurs withe combretastatin A-4 and podophyllotoxin. Because the mol. structure of curacin A is so different from that of previously described colchicine-site drugs (e.g., there is no arom. moiety, and there are only two conjugated double bonds in its linear hydrocarbon chain), we have been examg. the activities of natural isomers and synthetic derivs. So far, only modest enhancement or redn. of activity has been obsd. with a variety of structural changes.

IT **117048-59-6**, Combretastatin A4
RL: BPR (Biological process); BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study); PROC (Process)
(interaction of curacin A and analogs with colchicine site of tubulin)

RN 117048-59-6 CAPLUS
CN Phenol, 2-methoxy-5-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



L24 ANSWER 128 OF 157 CAPLUS COPYRIGHT 2003 ACS (Continued)

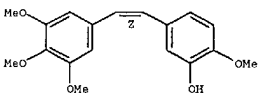
L24 ANSWER 129 OF 157 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1995:741422 CAPLUS
DOCUMENT NUMBER: 124:116940
TITLE: Antineoplastic Agents. 291. Isolation and Synthesis of Combretastatins A-4, A-5, and A-6. [Erratum to document cited in CA122:290568]
AUTHOR(S): Pettit, George R.; Singh, Sheo Bux; Boyd, Michael R.; Hamel, Ernest; Pettit, Robin K.; Schmidt, Jean M.; Hogan, Fiona
CORPORATE SOURCE: Cancer Research Institute and Dept.of Chemistry, Arizona State Univ., Tempe, AZ, 85287-1604, USA
SOURCE: Journal of Medicinal Chemistry (1995), 38(15), 2994
CODEN: JMCMAR; ISSN: 0022-2623
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The errors were not reflected in the abstr. or the index entries.

IT **117048-59-6P**, Combretastatin A-4
RL: BAC (Biological activity or effector, except adverse); BOC (Biological occurrence); BSU (Biological study, unclassified); PRP (Properties); PUR (Purification or recovery); SPN (Synthetic preparation); BIOL (Biological study); OCCU (Occurrence); PREP (Preparation)
(isolation, prepn., and biol. activity of combretastatins A-4, A-5, and A-6 (Erratum))

RN 117048-59-6 CAPLUS
CN Phenol, 2-methoxy-5-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

Double bond geometry as shown.

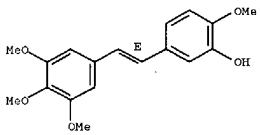


IT **117048-62-1P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(isolation, prepn., and biol. activity of combretastatins A-4, A-5, and A-6 (Erratum))

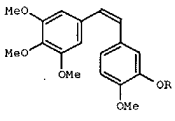
RN 117048-62-1 CAPLUS
CN Phenol, 2-methoxy-5-[(1E)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

Double bond geometry as shown.

L24 ANSWER 129 OF 157 CAPLUS COPYRIGHT 2003 ACS (Continued)



L24 ANSWER 130 OF 157 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1995:661775 CAPLUS
DOCUMENT NUMBER: 123:227731
TITLE: Antineoplastic agents. 322. Synthesis of combretastatin A-4 prodrugs
AUTHOR(S): Pettit, George R.; Temple, Carroll, Jr.; Narayanan, Ven L.; Varma, Ravi; Simpson, Michael J.; Boyd, Michael R.; Rener, Gregory A.; Bansal, Namita
CORPORATE SOURCE: Cancer Research Institute and Department of Chemistry, Arizona State University, Temple, AZ, 85287-1604, USA
SOURCE: Anti-Cancer Drug Design (1995), 10(4), 299-309
CODEN: ACDDEA; ISSN: 0266-9536
PUBLISHER: Oxford University Press
DOCUMENT TYPE: Journal
LANGUAGE: English
GI



I

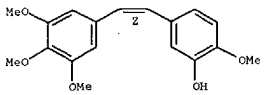
AB Combretastatin A-4 (I, R = H), the principal cancer cell growth-inhibitory constituent of the Zulu medicinal plant (Combretum caffrum, has been undergoing preclin. development. However, the very limited water soly. of this phenol has complicated drug formation. Hence, derivs. of the combretastatin A-4 3'-phenol group were prepd. for evaluation as possible water-sol. prodrugs. As obsd. for combretastatin A-4, the sodium salt (I, R = Na), potassium salt (I, R = K), and hemisuccinic acid ester (I, R = COCH2CH2CO2H) derivs. were essentially insol. in water. Indeed, these substances regenerated combretastatin A-4 upon reaction with water. A series of other simple derivs., e.g. I [R = COCH(NH2)CH2CH2CO2H], proved unsatisfactory in terms of water soly. or stability, or both. The most sol. derivs. evaluated included the ammonium [I, R = P(O)(OH)ONH4], and potassium [I, R = P(O)(OK)2] and sodium [I, R = P(O)(ONa)2] phosphate salts, where the latter two proved most stable and suitable. Both the potassium and sodium phosphate derivs. of combretastatin A-4 were also found to exhibit the requisite biol. properties necessary for a useful prodrug. The sodium phosphate salt was selected for drug formulation and further pre-clin. development.

IT **117048-59-6**, Combretastatin A-4
RL: RCT (Reactant); RACT (Reactant or reagent)
(synthesis of combretastatin A-4 prodrugs as antineoplastic agents)

RN 117048-59-6 CAPLUS
CN Phenol, 2-methoxy-5-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

Double bond geometry as shown.

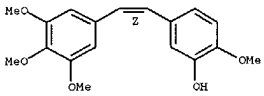
L24 ANSWER 130 OF 157 CAPLUS COPYRIGHT 2003 ACS (Continued)



IT **168555-63-3P 168555-67-7P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(synthesis of combretastatin A-4 prodrugs as antineoplastic agents)

RN 168555-63-3 CAPLUS
CN Phenol, 2-methoxy-5-[2-(3,4,5-trimethoxyphenyl)ethenyl]-, sodium salt, (Z)- (9CI) (CA INDEX NAME)

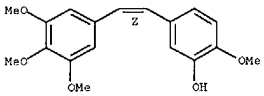
Double bond geometry as shown.



● Na

RN 168555-67-7 CAPLUS
CN Phenol, 2-methoxy-5-[2-(3,4,5-trimethoxyphenyl)ethenyl]-, potassium salt, (Z)- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



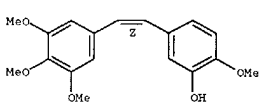
● K

L24 ANSWER 131 OF 157 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1995:619726 CAPLUS
DOCUMENT NUMBER: 123:47372
TITLE: The interaction with tubulin of a series of stilbenes based on combretastatin A-4
AUTHOR(S): Woods, J A.; Hadfield, J A.; Pettit, G R.; Fox, B W.; McGown, A T.
CORPORATE SOURCE: Paterson Institute Cancer Research, Christie Hospital, Manchester, M20 9BX, UK
SOURCE: British Journal of Cancer (1995), 71(4), 705-11
CODEN: BJCAAI; ISSN: 0007-0920
DOCUMENT TYPE: Journal
LANGUAGE: English
AB A series of stilbenes, based on combretastatin A-4, were synthesized. A structure-activity study was carried out to characterize the interaction of these agents with tubulin. The substitution of small alkyl substituents for the 4'-MeO group of combretastatin A-4 and the loss of the 3'-OH group does not have a major effect on the interaction with tubulin. Trans-Stilbenes bound tubulin, but did not inhibit microtubule assembly. An idealized structure for a tubulin-binding agent of this type is proposed. The antitumor cytotoxicity of the compds. is also discussed.

IT **117048-59-6DP**, Combretastatin A-4, analogs
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PRP (Properties); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(interaction of combretastatin A-4-related stilbenes with tubulin)

RN 117048-59-6 CAPLUS
CN Phenol, 2-methoxy-5-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

Double bond geometry as shown.

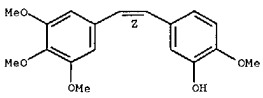


L24 ANSWER 132 OF 157 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1995:538890 CAPLUS
DOCUMENT NUMBER: 122:290568
TITLE: Antineoplastic Agents. 291. Isolation and Synthesis of Combretastatins A-4, A-5, and A-6
AUTHOR(S): Pettit, George R.; Singh, Sheo Bux; Boyd, Michael R.; Hamel, Ernest; Pettit, Robin K.; Schmidt, Jean M.; Hogan, Fiona
CORPORATE SOURCE: Cancer Research Institute and Department of Chemistry, Arizona State University, Tempe, AZ, 85287-1604, USA
SOURCE: Journal of Medicinal Chemistry (1995), 38(10), 1666-72
CODEN: JMCMAR; ISSN: 0022-2623
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The title compds. (Z)-3,4,5-(MeO)3C6H2CH:CHC6H3(OMe)OH-4,3 (I) and (Z)- and (E)-3,4,5-HO(MeO)2C6H2CH:CHC6H3(OMe)2-3,4 (II) were isolated from Combretum caffrum. They were also prepd. by Wittig reactions. I is the most potent cell growth inhibitor of the series. It is also the most potent inhibitor of colchicine binding to tubulin. I and II also inhibit the growth of Neisseria gonorrheae, but have no fungicidal activity.

IT **117048-59-6P**, Combretastatin A-4
RL: BAC (Biological activity or effector, except adverse); BOC (Biological occurrence); BSU (Biological study, unclassified); PRP (Properties); PUR (Purification or recovery); SPN (Synthetic preparation); BIOL (Biological study); OCCU (Occurrence); PREP (Preparation)
(isolation, prepn., and biol. activity of combretastatins A-4, A-5, and A-6)

RN 117048-59-6 CAPLUS
CN Phenol, 2-methoxy-5-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

Double bond geometry as shown.

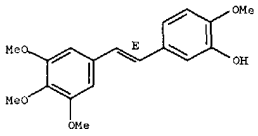


IT **117048-62-1P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(isolation, prepn., and biol. activity of combretastatins A-4, A-5, and A-6)

RN 117048-62-1 CAPLUS
CN Phenol, 2-methoxy-5-[(1E)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

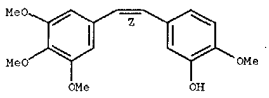
Double bond geometry as shown.

L24 ANSWER 132 OF 157 CAPLUS COPYRIGHT 2003 ACS (Continued)



L24 ANSWER 133 OF 157 CAPLUS COPYRIGHT 2003 ACS (Continued)

Double bond geometry as shown.



L24 ANSWER 133 OF 157 CAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 1995:532227 CAPLUS
DOCUMENT NUMBER: 122:256433
TITLE: Estrogens as antimitotic agents
INVENTOR(S): D'Amato, Robert John; Folkman, Moses Judah
PATENT ASSIGNEE(S): Children's Medical Center Corp., USA
SOURCE: PCT Int. Appl., 53 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9504535	A1	19950216	WO 1994-US8767	19940802
W: AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, ES, FI, GB, GE, HU, JP, KE, KG, KP, KR, KZ, LK, LT, LU, LV, MD, MG, MN, MW, NL, NO, NZ, PL, PT, RO, RU, SD, SE, SI, SK, TJ, TT, UA, UZ, VN				
RW: KE, MW, SD, AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
US 5504074	A	19960402	US 1993-102767	19930806
CA 2168850	AA	19950216	CA 1994-2168850	19940802
AU 9474509	A1	19950228	AU 1994-74509	19940802
EP 713393	A1	19960529	EP 1994-924120	19940802
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE				
JP 09501433	T2	19970210	JP 1994-506502	19940802
US 5661143	A	19970826	US 1995-571265	19951212
US 5892069	A	19990406	US 1997-838699	19970425
US 6528676	B1	20030304	US 1999-243158	19990202
US 2002165212	A1	20021107	US 2002-77142	20020215
US 2002119959	A1	20020829	US 2002-80076	20020221
US 2003055029	A1	20030320	US 2002-255652	20020925
US 2003096800	A1	20030522	US 2002-280831	20021025

PRIORITY APPLN. INFO.:
US 1993-102767 A 19930806
WO 1994-US8767 W 19940802
US 1995-571265 A3 19951212
US 1997-838699 A3 19970425
US 1998-19975 B1 19980206
US 1999-243158 B1 19990202
US 1999-436610 B1 19991109
US 2000-580897 A1 20000530
US 2001-780650 A1 20010212

OTHER SOURCE(S): MARPAT 122:256433

AB Drugs for treating mammalian diseases characterized by abnormal cell mitosis by administering estradiol derivs., colchicine or combretastatin A-4 are described. The inhibition of tubulin polymn. by 2-methoxyestradiol (75 .mu.M) in a mixt. contg. monosodium glutamate, DMSO and MgCl2 was demonstrated.

IT **117048-59-6**, Combretastatin A-4
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(estrogens as antimitotic agents)

RN 117048-59-6 CAPLUS

CN Phenol, 2-methoxy-5-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

L24 ANSWER 134 OF 157 CAPLUS COPYRIGHT 2003 ACS

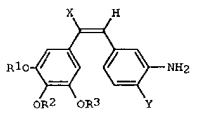
ACCESSION NUMBER: 1995:520466 CAPLUS
DOCUMENT NUMBER: 122:265183
TITLE: Preparation of stilbene derivatives as carcinostatic agents.
INVENTOR(S): Ohsumi, Koji; Tsuji, Takashi; Morinaga, Yoshihiro; Ohishi, Kazuo
PATENT ASSIGNEE(S): Ajinomoto Co., Inc., Japan
SOURCE: Eur. Pat. Appl., 14 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 641767	A1	19950308	EP 1994-306522	19940905
EP 641767	B1	19981223		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE				
AT 174899	E	19990115	AT 1994-306522	19940905
ES 2126068	T3	19990316	ES 1994-306522	19940905
JP 07228558	A2	19950829	JP 1994-236046	19940906
JP 3045017	B2	20000522		
CA 2131683	AA	19950309	CA 1994-2131683	19940908
CN 1105967	A	19950802	CN 1994-116204	19940908
CN 1035996	B	19971001		
US 5525632	A	19960611	US 1994-302210	19940908
US 5731353	A	19980324	US 1996-613005	19960308

PRIORITY APPLN. INFO.:
JP 1993-223573 A 19930908
JP 1993-322832 A 19931221
US 1994-302210 A1 19940908

OTHER SOURCE(S): CASREACT 122:265183; MARPAT 122:265183

GI



I

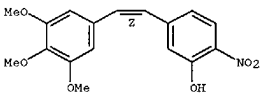
AB The prepn. of stilbenes I (R1, R2, R3 = C1-3 alkyl; X = H, cyano; Y = C1-3 alkyloxy, C1-6 alkyl, halo), which are low in toxicity, but are water sol. and effective as carcinostatics, is described. Thus, stilbene I (R1 = R2 = R3 = Me, X = H, Y = MeO), prepd. by condensation of 4-methoxy-3-nitrobenzaldehyde with 3,4,5-trimethoxybenzyltriphenylphosphonium bromide and subsequent redn. of the nitro group, inhibited the growth of mouse P388 leukemia cells with an IC50 = 0.2 ng/mL (comparable to combretastatin A-4).

IT **117048-59-6DP**, Combretastatin A-4, analogs
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of stilbene derivs. as carcinostatic agents)

RN 117048-59-6 CAPLUS

L24 ANSWER 137 OF 157 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1995:21047 CAPLUS
DOCUMENT NUMBER: 122:81695
TITLE: Potential Photoaffinity Labels for Tubulin. Synthesis and Evaluation of Diazocyclohexadienone and Azide Analogs of Colchicine, Combrétastatin, and 3,4,5-Trimethoxybiphenyl
AUTHOR(S): Olszewski, John D.; Marshalla, Mary; Sabat, Michal; Sundberg, Richard J.
CORPORATE SOURCE: Department of Chemistry, University of Virginia, Charlottesville, VA, 22901, USA
SOURCE: Journal of Organic Chemistry (1994), 59(15), 4285-96
CODEN: JOCEAH; ISSN: 0022-3263
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Analogs of tubulin assembly inhibitors such as colchicine, combretastatin, and 3,4,5-trimethoxybiphenyl which incorporate a 6-diazo-2,4-cyclohexadienone (o-quinone diazide) ring have been synthesized and characterized. Compds. in which the cyclohexadienone oxygen is approx. isostructural with carbonyl or hydroxy functions of the parent compds. exhibit good activity in the tubulin assembly inhibition assay. 2'-Alkyl-4'-azido-3,4,5-trimethoxy-1,1'-biphenyls also show good activity as tubulin assembly inhibitors.
IT **156878-52-3P 156878-53-4P 156878-54-5P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(prepn. and reaction of, in prepn. of diazocyclohexadienone-contg. tubulin assembly inhibitors)
RN 156878-52-3 CAPLUS
CN Phenol, 2-nitro-5-[2-(3,4,5-trimethoxyphenyl)ethenyl]-, (Z)- (9CI) (CA INDEX NAME)

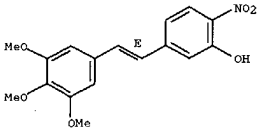
Double bond geometry as shown.



RN 156878-53-4 CAPLUS
CN Phenol, 2-nitro-5-[2-(3,4,5-trimethoxyphenyl)ethenyl]-, (E)- (9CI) (CA INDEX NAME)

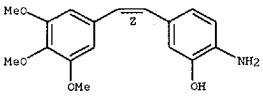
Double bond geometry as shown.

L24 ANSWER 137 OF 157 CAPLUS COPYRIGHT 2003 ACS (Continued)



RN 156878-54-5 CAPLUS
CN Phenol, 2-amino-5-[2-(3,4,5-trimethoxyphenyl)ethenyl]-, (Z)- (9CI) (CA INDEX NAME)

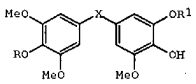
Double bond geometry as shown.



L24 ANSWER 138 OF 157 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1994:473872 CAPLUS
DOCUMENT NUMBER: 121:73872
TITLE: Combretastatin derivatives with antitumor activity, and process for the preparation thereof
INVENTOR(S): Pelizzoni, Francesca; Colombo, Roberto; D'Incalci, Maurizio; Verotta, Luisella
PATENT ASSIGNEE(S): Italy
SOURCE: PCT Int. Appl., 28 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9405682	A1	19940317	WO 1993-EP2173	19930816
W: AU, BY, CA, FI, HU, JP, KR, KZ, NZ, PL, RU, UA, US				
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
AU 9349479	A1	19940329	AU 1993-49479	19930816
ZA 9306311	A	19940323	ZA 1993-6311	19930827
PRIORITY APPLN. INFO.:			IT 1992-MI2033 A	19920831
			WO 1993-EP2173 W	19930816

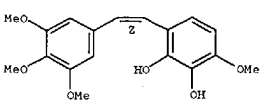
OTHER SOURCE(S): MARPAT 121:73872
GI



I

AB Combretastatin derivs. I (R = H, Me; R' = H, .beta.-D-glucopyranose (provided that when R is Me, R' .noteq. H); A = CH2CH2, CH:CH] with antitumor activity are disclosed. Also included are a process for the extn. and isolation of I from Combretum kraussii, pharmaceutical compns. for antitumor use, and prepn. of the pharmaceutical compns.
IT **109971-63-3P 156085-79-9P**
RL: PUR (Purification or recovery); PREP (Preparation)
(isolation of, from Combretum kraussii, for antitumor agent)
RN 109971-63-3 CAPLUS
CN 1,2-Benzenediol, 3-methoxy-6-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]-(9CI) (CA INDEX NAME)

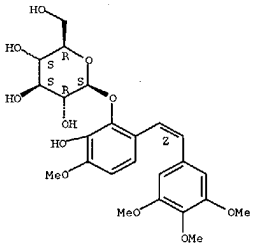
Double bond geometry as shown.



RN 156085-79-9 CAPLUS

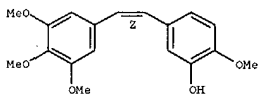
L24 ANSWER 138 OF 157 CAPLUS COPYRIGHT 2003 ACS (Continued)
CN .beta.-D-Glucopyranoside, 2-hydroxy-3-methoxy-6-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]phenyl (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).
Double bond geometry as shown.

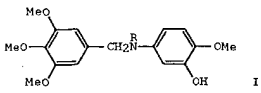


L24 ANSWER 139 OF 157 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1994:473249 CAPLUS
DOCUMENT NUMBER: 121:73249
TITLE: Increase in the chemically-induced differentiation of human leukemia cell lines by tubulin disruptors
AUTHOR(S): Nakajima, Osamu; Sugishita, Yasuko; Hashimoto, Yuichi; Iwasaki, Shigeo
CORPORATE SOURCE: Inst. Mol. Cellular Biosciences, University Tokyo, Tokyo, 113, Japan
SOURCE: Biological & Pharmaceutical Bulletin (1994), 17(5), 742-4
CODEN: BPBLEO; ISSN: 0918-6158
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The effect of various structural functional tubulin disruptors (including colchicine-type disruptors, vinblastine, rhizoxin, maytansine, peptide-type disruptors, and taxol) on the chem. induced differentiation of human leukemia cell lines (HL-60 and K562) was examd. As differentiation-inducing agents, 12-O-tetradecanoylphorbol-13-acetate (TPA) was used for the differentiation of both HL-60 and K562 to monocyte/macrophages, retinoids were used for the differentiation of HL-60 to mature granulocytes, and hemin was used for the erythroid differentiation of K562. All the tubulin disruptors investigated increased the chem.-induced differentiation of HL-60 and K562 cell lines to the cognate mature cell types, regardless of the nature of the differentiation.
IT **117048-59-6**, Combretastatin A-4
RL: BIOL (Biological study)
(chem. induced leukemia cell differentiation increase by, of humans, as tubulin disruptor)
RN 117048-59-6 CAPLUS
CN Phenol, 2-methoxy-5-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



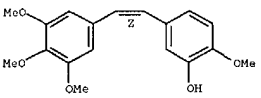
L24 ANSWER 140 OF 157 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1994:426244 CAPLUS
DOCUMENT NUMBER: 121:26244
TITLE: Synthesis and anti-tubulin activity of aza-combretastatins
AUTHOR(S): Shirai, Ryuichi; Tokuda, Kazuyoshi; Koiso, Yukiko; Iwasaki, Shigeo
CORPORATE SOURCE: Inst. Mol. Cell. Biosci., Univ. Tokyo, Tokyo, 113, Japan
SOURCE: Bioorganic & Medicinal Chemistry Letters (1994), 4(5), 699-704
CODEN: BMCLE8; ISSN: 0960-894X
DOCUMENT TYPE: Journal
LANGUAGE: English
GI



I

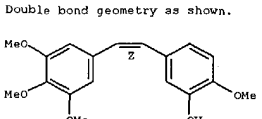
AB A series of aza-combretastatins was synthesized and their activity against microtubule assembly was evaluated. N-benzylaniline analogs with a variety of side chains (I, R = e.g., H or alkyl) showed moderate to excellent inhibitory activity while benzanilide analogs had little activity.
IT **117048-59-6**, Combretastatin A-4
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(antitubulin activity of, aza analogs in relation to)
RN 117048-59-6 CAPLUS
CN Phenol, 2-methoxy-5-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



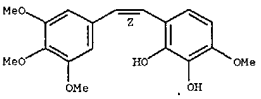
L24 ANSWER 141 OF 157 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1994:290371 CAPLUS
DOCUMENT NUMBER: 120:290371
TITLE: 2-Methoxyestradiol, an endogenous mammalian metabolite, inhibits tubulin polymerization by interacting at the colchicine site
AUTHOR(S): D'Amato, Robert J.; Lin, Chii M.; Flynn, Evelyn; Folkman, Judah; Hamel, Ernest
CORPORATE SOURCE: Dep. Surg. Res., Harvard Med. Sch., Boston, MA, 02115, USA
SOURCE: Proceedings of the National Academy of Sciences of the United States of America (1994), 91(9), 3964-8
CODEN: PNASA6; ISSN: 0027-8424
DOCUMENT TYPE: Journal
LANGUAGE: English
AB A metabolite of estradiol, 2-methoxyestradiol (2ME), inhibits angiogenesis in the chicken embryo chorioallantoic membrane assay. Since 2ME causes mitotic perturbations, the authors examd. its interactions with tubulin. In the authors' std. 1.0M glutamate system (plus 1.0 mM MgCl2 at 37.degree.), superstoichiometric concns. (relative to tubulin) of 2ME inhibited the nucleation and propagation phases of tubulin assembly but did not affect the reaction extent. Although polymer formed in the presence of 2ME was more cold-stable than control polymer, morphol. was little changed. Under suboptimal reaction conditions (0.8M glutamate/no MgCl2 at 26.degree.), substoichiometric 2ME totally inhibited polymn. No other estrogenic compd. was as effective as 2ME as an inhibitor of polymn. or of the binding of colchicine to tubulin. Inhibition of colchicine binding was competitive (Ki, 22 .mu.M). Thus, a mammalian metabolite of estradiol binds to the colchicine site of tubulin and, depending on reaction conditions, either inhibits assembly or seems to be incorporated into a polymer with altered stability properties.
IT **117048-59-6**, Combretastatin A-4
RL: BIOL (Biological study)
(tubulin polymn. inhibition by)
RN 117048-59-6 CAPLUS
CN Phenol, 2-methoxy-5-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



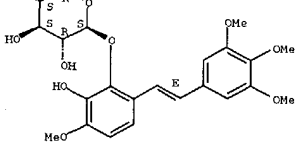
L24 ANSWER 142 OF 157 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1993:621659 CAPLUS
DOCUMENT NUMBER: 119:221659
TITLE: Cell growth inhibitor constituents from Combretum krausssii
AUTHOR(S): Pelizzoni, F.; Verotta, L.; Rogers, C. B.; Colombo, R.; Pedrotti, B.; Balconi, G.; Erba, E.; D'Incalci, M.
CORPORATE SOURCE: Dip. Chim. Org. INd., Milano, 20133, Italy
SOURCE: Natural Product Letters (1993), 1(4), 273-80
CODEN: NPLEEF; ISSN: 1057-5634
DOCUMENT TYPE: Journal
LANGUAGE: English
AB New and known combretastatins and their 2'-O-glucosides have been isolated from seeds of Combretum kraussi (Hochst.) (Combretaceae). They showed in vitro cytotoxicity and influenced the tubulin polymn.
IT **109971-63-3 150934-29-5**
RL: BIOL (Biological study)
(from Combretum krasussii, isolation and structure of)
RN 109971-63-3 CAPLUS
CN 1,2-Benzenediol, 3-methoxy-6-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



RN 150934-29-5 CAPLUS
CN .beta.-D-Glucopyranoside, 2-hydroxy-3-methoxy-6-[2-(3,4,5-trimethoxyphenyl)ethenyl]phenyl, (E)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

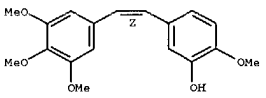


L24 ANSWER 143 OF 157 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1993:225093 CAPLUS
DOCUMENT NUMBER: 118:225093
TITLE: In vitro evaluation of the antineoplastic activity of combretastatin A4, a natural product from Combretum caffrum (arid shrub)
AUTHOR(S): El-Zayat, A. Atef Ebrahim; Degen, Donna; Drabek, Sonya; Clark, Gary M.; Pettit, George R.; Von Hoff, Daniel D.
CORPORATE SOURCE: Cancer Ther. Res. Cent., San Antonio, TX, 78229, USA
SOURCE: Anti-Cancer Drugs (1993), 4(1), 19-25
CODEN: ANTDEV; ISSN: 0959-4973
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The cytotoxic activity of combretastatin A4 was tested in radiometric and human tumor cloning assays against 8 different tumor cell lines and against 15 patient tumors in the human tumor cloning assay. To test the preferential cytotoxicity of combretastatin A4 against tumor cells vs. nontumor cells, it was also tested in the radiometric assay against both normal human diploid fibroblasts and human bone marrow cells. Of the 8 cell lines used, combretastatin A4 showed preferential cytotoxicity for six of them. In addn., combretastatin A4 showed a concn.-dependent cytotoxicity against a variety of human tumors. Based on these data, combretastatin A4 should be further tested in in vivo preclin. models.

IT **117048-59-6**, Combretastatin A4
RL: BIOL (Biological study)
(neoplasm of humans inhibition by)
RN 117048-59-6 CAPLUS
CN Phenol, 2-methoxy-5-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

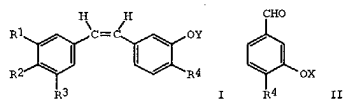
Double bond geometry as shown.



L24 ANSWER 144 OF 157 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1993:101642 CAPLUS
DOCUMENT NUMBER: 118:101642
TITLE: Preparation of combretastatin A4 analogs as neoplasm inhibitors
INVENTOR(S): Rathbone, Daniel Lee; Slack, John Alfred; Griffin, Roger John; Quarterman, Charmaine Paulina
PATENT ASSIGNEE(S): Aston Molecules Ltd., UK
SOURCE: PCT Int. Appl., 29 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9216486	A1	19921001	WO 1992-GB498	19920319
W: AU, CA, JP, US				
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LU, MC, NL, SE				
AU 9213719	A1	19921021	AU 1992-13719	19920319
PRIORITY APPLN. INFO.:			GB 1991-6177	19910322
			WO 1992-GB498	19920319

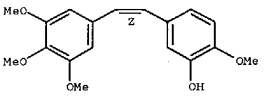
OTHER SOURCE(S): MARPAT 118:101642
GI



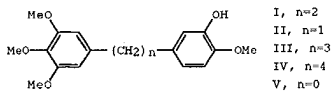
AB Title compds. I (R1-R4 = alkoxy; Y = H, phosphate, phosphate deriv., amino acid carbamate, carbohydrate deriv., polyhydroxylated group) were prepd. via Wittig olefination of benzaldehyde deriv. II (X = protecting group) by a trialkoxybenzylphosphonium halide. I, e.g., water sol. combretastatin A4 analogs, are neoplasm inhibitors (no data). Thus, 3-hydroxy-4-methoxybenzaldehyde was protected by thexyldimethylsilyl chloride then olefinated by 3,4,5-trimethoxybenzylphosphonium bromide (prepn. given). The product was deprotected by Bu4NF to give combretastatin A4. This was treated with di-tert-Bu N,N-diethylphosphoramidite and 1H-tetrazole in THF, cooled to -70.degree., then treated, with MCPBA to give combretastatin A4 phosphate bis(tert-butyl) ester in 77% yield.

IT **117048-59-6P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of, as neoplasm inhibitor)
RN 117048-59-6 CAPLUS
CN Phenol, 2-methoxy-5-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

L24 ANSWER 144 OF 157 CAPLUS COPYRIGHT 2003 ACS (Continued)
Double bond geometry as shown.



L24 ANSWER 145 OF 157 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1992:143282 CAPLUS
DOCUMENT NUMBER: 116:143282
TITLE: Synthesis of alkoxy-substituted diaryl compounds and correlation of ring separation with inhibition of tubulin polymerization: differential enhancement of inhibitory effects under suboptimal polymerization reaction conditions
AUTHOR(S): Getahun, Zelleka; Jurd, Leonard; Chu, Ping S.; Lin, Chii M.; Hamel, Ernest
CORPORATE SOURCE: Lab. Mol. Pharmacol., Natl. Cancer Inst., Bethesda, MD, 20892, USA
SOURCE: Journal of Medicinal Chemistry (1992), 35(6), 1058-67
CODEN: JMCMAR; ISSN: 0022-2623
DOCUMENT TYPE: Journal
LANGUAGE: English
GI



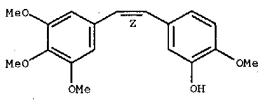
I, n=2
II, n=1
III, n=3
IV, n=4
V, n=0

AB A no. of cytostatic compds. which can be described as diaryl, inhibit tubulin polymn., cause cells to accumulate in mitotic arrest, and competitively inhibit the binding of colchicine to tubulin. They differ, however, in the sepn. of the 2 aryl moieties. To attempt to understand this variability a series of analogs modeled on a benzodioxole series and on a combretastatin series which differed only in the no. of methylene units (ranging from 0-4) sepg. the aryl moieties were prepd. These compds. were evaluated for their effects on tubulin polymn., colchicine binding, and the growth of L1210 murine leukemia cells. In terms of inhibitory effects on tubulin polymn., for the combretastatin series there was an optimal sepn. of the 2 Ph rings by a 2-carbon bridge (I), with progressively decreasing inhibitory activity when the sepn. was by 1 carbon (II), 3 carbons (III), or 4 carbons (IV) (the biphenyl analog V was inactive). The benzodioxole series, however, did not permit the generalizatiin of this finding, because the least active agents prepd. had a 2-carbon bridge, while those with 1 and 3-carbon bridges were nearly equiv. in potency. Submicromolar IC50 values for inhibition of L1210 cell growth were only obtained for II (IC50, 0.2 .mu.M), I (0.07 .mu.M), and III (0.4 .mu.M). While evaluating the effects of these agents on tubulin polymn., with the combretastatin series and with several std. agents apparent potency (in terms of IC50 values) was always lower if the reaction was performed at 30.degree., with 0.25 mM MgCl2, than at 37.degree., with 1.0 mM MgCl2. This enhancement of IC50 values in the former system as compared with the latter was particularly dramatic for the less active agents (e.g., IV) as compared with the more active (e.g., I).

IT **117048-59-6**, Combretastatin A-4
RL: BIOL (Biological study)
(binding of colchicine to and polymn. of tubulins inhibition by)
RN 117048-59-6 CAPLUS
CN Phenol, 2-methoxy-5-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

L24 ANSWER 145 OF 157 CAPLUS COPYRIGHT 2003 ACS (Continued)

Double bond geometry as shown.



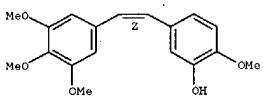
L24 ANSWER 146 OF 157 CAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 1992:75795 CAPLUS
DOCUMENT NUMBER: 116:75795
TITLE: Investigation of the mechanism of the interaction of tubulin with derivatives of 2-styrylquinazolin-4(3H)-one
AUTHOR(S): Lin, Chii M.; Kang, Gil Jong; Roach, Mary Carmen; Jiang, Jack B.; Hesson, David P.; Luduena, Richard F.; Hamel, Ernest
CORPORATE SOURCE: Lab. Mol. Pharmacol., Natl. Cancer Inst., Bethesda, MD, 20892, USA
SOURCE: Molecular Pharmacology (1991), 40(5), 827-32
CODEN: MOPMA3; ISSN: 0026-895X
DOCUMENT TYPE: Journal
LANGUAGE: English

AB A new class of antimitotic agents, derivs. of 2-styrylquinazolin-4(3H)-one (SQZ), was recently described [J. Med. Chem. 33:1721-1728 (1990)]. Because they appeared to interact at a new ligand binding site on tubulin, the authors attempted to det. their mechanism of action as inhibitors of tubulin polymn. Although in initial studies inhibition of colchicine binding was negligible, substantial and competitive inhibition of this reaction could be demonstrated with very short incubation times (<5 min), provided that a relatively low colchicine to tubulin ratio was used. The initial apparent failure to inhibit colchicine binding resulted from extremely rapid binding to tubulin and dissocn. from tubulin by the SQZ derivs., in comparison with the slow, temp.-dependent, poorly reversible binding of colchicine. The most inhibitory of the SQZ derivs. in the colchicine binding assay was 6-methyl-2-styrylquinazolin-4(3H)-one (NSC 379310), and its interaction with tubulin, particularly as an inhibitor of colchicine binding, was compared with that of 2-methoxy-5-(2',3',4'-trimethoxyphenyl)tropone (MTPT), because the binding parameters of MTPT with tubulin have been well described. The data indicate that NSC 379310 binds to tubulin and dissocs. from the protein about 3 times as rapidly as MTPT. The other SQZ derivs. with equal or greater potency as inhibitors of tubulin polymn. but apparently less potency as inhibitors of colchicine binding presumably bind to and/or dissoc. from tubulin even more rapidly than does NSC 379310.

IT **117048-59-6**
RL: BIOL (Biological study)
(tubulin binding inhibition by, antimitotic mechanism in relation to)
RN 117048-59-6 CAPLUS
CN Phenol, 2-methoxy-5-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

Double bond geometry as shown.

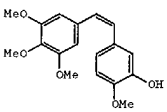


L24 ANSWER 147 OF 157 CAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 1991:589740 CAPLUS
DOCUMENT NUMBER: 115:189740
TITLE: Combretastatin A-4 from Combretum caffrum
INVENTOR(S): Pettit, George R.; Singh, Sheo B.
PATENT ASSIGNEE(S): Arizona Board of Regents, USA
SOURCE: U.S., 7 pp. Cont.-in-part of U.S. Ser. No. 590.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 4996237	A	19910226	US 1988-158866	19880222
CA 1338645	A1	19961015	CA 1987-554733	19871217
JP 63233939	A2	19880929	JP 1987-327577	19871225
JP 2558131	B2	19961127		
ES 2038747	T3	19930801	ES 1988-300064	19880106
US 5409953	A	19950425	US 1992-832998	19920210
US 5569786	A	19961029	US 1994-340156	19941115
PRIORITY APPLN. INFO.:			US 1987-590	19870106
			US 1992-832998	19920210

GI



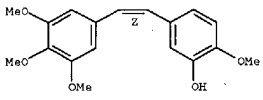
I

AB Combretastatin A-4 (I) is extd. from the stem wood of C. caffrum. I is a powerful inhibitor of tubulin polymn. (IC50 2-3.mu.M) and of the growth of murine lymphocytic leukemia (L1210 and P388; ED50 <0.003 mg/mL) and human colon cancer cell lines (HoLo, etc.; ED50 <0.01 .mu.g/mL). The structure assigned by spectral techniques was confirmed by synthesis. Capsule, tablet, powder, parenteral, and other formulations are presented.

IT **117048-59-6P**, Combretastatin A-4
RL: SPN (Synthetic preparation); PREP (Preparation)
(prepn. and isolation of, from Combretum caffrum, as neoplasm inhibitor)
RN 117048-59-6 CAPLUS
CN Phenol, 2-methoxy-5-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

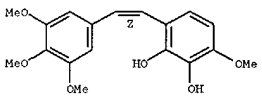
Double bond geometry as shown.

L24 ANSWER 147 OF 157 CAPLUS COPYRIGHT 2003 ACS (Continued)



L24 ANSWER 148 OF 157 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1991:484835 CAPLUS
DOCUMENT NUMBER: 115:84835
TITLE: Quantitative structure-activity relationship analysis of combretastatins: a class of novel antimitotic agents
AUTHOR(S): Nandy, Partha; Banerjee, Samitendu; Gao, Hua; Hui, Mary B. Y.; Lien, Eric J.
CORPORATE SOURCE: Sch. Pharm., Univ. South. California, Los Angeles, CA, 90033, USA
SOURCE: Pharmaceutical Research (1991), 8(6), 776-81
CODEN: PHREEB; ISSN: 0724-8741
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Combretastatins and their synthetic analogs had structural features resembling those of colchicine and also have similar modes of action. The cytotoxicity of combrestatins against the murine leukocyte cell line L1210 was correlated with physicochem. parameters such as the summation of the Hansch-Fujita .pi. const., which was used as an index of lipophilicity of the substituent groups on ring A (.SIGMA..pi.a) and ring B (.SIGMA..pi.b), the vector summation of the group dipole moments of ring A (.SIGMA..mu.a) and ring B (.SIGMA..mu.b), the nature of the linker chain between ring A and ring B (Bt-L), indicator parameters (NOH)a and (NOH)b, which represent the no. of hydroxyl groups on ring A and ring B, resp., and the summation of .pi. values of the substituents on the linker (.SIGMA..pi.L). Cytotoxicity correlated well with (.SIGMA..pi.b), (NOH)a, (Bt-L), and (.SIGMA..mu.b), and the dependency on (.SIGMA..pi.b) was parabolic.
IT **109971-63-3 117048-59-6 117048-62-1**
RL: BIOL (Biological study)
(antileukemic cytotoxicity and structure of)
RN 109971-63-3 CAPLUS
CN 1,2-Benzenediol, 3-methoxy-6-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

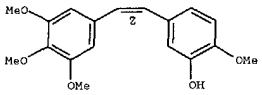
Double bond geometry as shown.



RN 117048-59-6 CAPLUS
CN Phenol, 2-methoxy-5-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

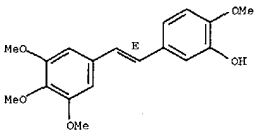
Double bond geometry as shown.

L24 ANSWER 148 OF 157 CAPLUS COPYRIGHT 2003 ACS (Continued)

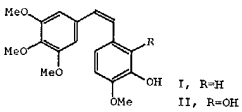


RN 117048-62-1 CAPLUS
CN Phenol, 2-methoxy-5-[(1E)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



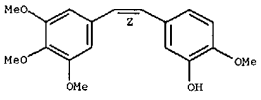
L24 ANSWER 149 OF 157 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1990:400240 CAPLUS
DOCUMENT NUMBER: 113:240
TITLE: Differential cytotoxicity of combretastatins A1 and A4 in two daunorubicin-resistant P388 cell lines
AUTHOR(S): McGown, Alan T.; Fox, Brian W.
CORPORATE SOURCE: Paterson Inst. Cancer Res., Christie Hosp., Withington/ Manchester, M20 9BX, UK
SOURCE: Cancer Chemotherapy and Pharmacology (1990), 26(1), 79-81
CODEN: CCPHDZ; ISSN: 0344-5704
DOCUMENT TYPE: Journal
LANGUAGE: English
GI



I, R=H
II, R=OH

AB Combretastatin A4 (I), a novel antimitotic agent was effective against two P388 cell lines with acquired resistance to daunorubicin. In contrast, combretastatin A1 (II) showed a high degree of cross-resistance. II was also more efficient at increasing intracellular daunorubicin concns. in both resistant cell lines. Neither agent was capable of altering anthracycline accumulation in the parental (sensitive) cell line. The cross-resistance to II occurs, at least in part, as a result of the increased affinity of the drug-efflux process operative in these resistant cells for II vs. I. Hence, I may play a role in the treatment of tumors with acquired resistance to the anthracycline antibiotics.
IT **117048-59-6**, Combretastatin A4
RL: PRP (Properties)
(cytotoxicity of, to multidrug-resistant tumor cell lines, combretastatin A1 in relation to)
RN 117048-59-6 CAPLUS
CN Phenol, 2-methoxy-5-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

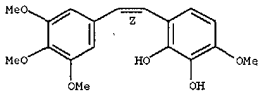
Double bond geometry as shown.



IT **109971-63-3**, Combretastatin A1
RL: PRP (Properties)
(cytotoxicity of, to multidrug-resistant tumor cell lines, combretastatin A4 in relation to)
RN 109971-63-3 CAPLUS

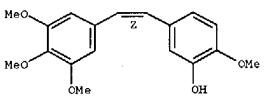
L24 ANSWER 149 OF 157 CAPLUS COPYRIGHT 2003 ACS (Continued)
CN 1,2-Benzenediol, 3-methoxy-6-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



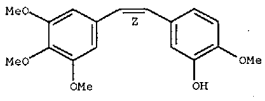
L24 ANSWER 150 OF 157 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1989:546274 CAPLUS
DOCUMENT NUMBER: 111:146274
TITLE: Structural and biochemical comparison of the antimitotic agents colchicine, combretastatin A4 and amphethinile
AUTHOR(S): McGown, A. T.; Fox, B. W.
CORPORATE SOURCE: Paterson Inst. Cancer Res., Christie Hosp. Holt Radium Inst., Withington/Manchester, M20 9BX, UK
SOURCE: Anti-Cancer Drug Design (1989), 3(4), 249-54
CODEN: ACDDEA; ISSN: 0266-9536
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The novel agents amphethinile and combretastatin A4 are shown to be very similar to colchicine in their interactions with purified tubulin. All 3 agents can inhibit tubulin assembly at similar treatment levels and have comparable affinity consts. for tubulin. Amphethinile and combretastatin A4 are capable of displacing colchicine but not vinblastine from tubulin. A comparison of the structures of these agents shows that whereas colchicine and combretastatin A4 contain a trimethoxybenzene group (a moiety also found in other colchicine-like agents such as podophyllotoxins and steganacin) no obvious similarity is seen from amphethinile. The 3-dimensional structures of these agents, detd. from either crystallog. data or by energy minimization procedures, show, however, that all 3 agents consist of 2 planar, or almost planar, ring systems which are tilted with respect to each other. Using computer graphic techniques it can be shown that their ring systems are superimposable and that the planar sections of each mol. are at an angle of 50-60.degree. to each other. It is proposed that the angular bicyclic structure of these agents is one detg. factor for their efficient binding to tubulin.
IT **117048-59-6**, NSC 817373
RL: BIOL (Biological study)
(tubulin binding by, structure in relation to)
RN 117048-59-6 CAPLUS
CN Phenol, 2-methoxy-5-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



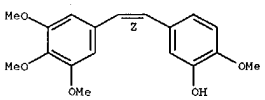
L24 ANSWER 151 OF 157 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1989:489891 CAPLUS
DOCUMENT NUMBER: 111:89891
TITLE: Antimitotic natural products combretastatin A-4 and combretastatin A-2: studies on the mechanism of their inhibition of the binding of colchicine to tubulin
AUTHOR(S): Lin, Chii M.; Ho, Holly H.; Pettit, George R.; Hamel, Ernest
CORPORATE SOURCE: Lab. Biochem. Pharmacol., Natl. Cancer Inst., Bethesda, MD, 20892, USA
SOURCE: Biochemistry (1989), 28(17), 6984-91
CODEN: BICHAW; ISSN: 0006-2960
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The mechanism of the binding of combretastatin A-4 (CS-A4) and combretastatin A-2 (CS-A2), isolated from Combretum caffrum, to tubulin was examd. indirectly by evaluating their effects on the binding of radiolabeled colchicine to the protein. There was rapid binding of both compds. to tubulin even at 0.degree. (binding was complete at the earliest times examd.), in contrast to the relatively slow and temp.-dependent binding of colchicine. Although the binding of the C. caffrum compds. to tubulin was quite tight, permitting ready isolation of near-stoichiometric amts. of drug-tubulin complex even in the absence of free drug, both CS-A4 and CS-A2 dissocd. rapidly from tubulin in the presence of high concns. of radiolabeled colchicine. Apparent rate consts. for drug dissocn. from tubulin at 37.degree. were 3.2 .times. 10-3/s for CS-A4, 4.8 .times. 10-3/s for CS-A2, and 2.9 .times. 10-5/s for colchicine (half-lives of 3.6, 2.4, and 405 min, resp.). Thus, the effectiveness of the C. caffrum compds. as antimitotic agents appears to derive primarily from the rapidity of their binding to tubulin. A new model for the colchicine binding site on tubulin is proposed which envisages A-ring and C-ring subsites in homologous locations on the 2 tubulin subunits, with Ph rings binding as well as or better than the tropolone ring of colchicine in the C-ring subsite.
IT **117048-59-6**, Combretastatin A4
RL: BIOL (Biological study)
(binding of, to tubulins, mechanism of)
RN 117048-59-6 CAPLUS
CN Phenol, 2-methoxy-5-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

Double bond geometry as shown.

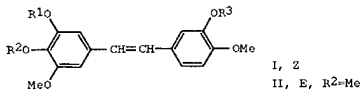


L24 ANSWER 152 OF 157 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1989:417138 CAPLUS
DOCUMENT NUMBER: 111:17138
TITLE: Structural and biochemical comparison of the anti-mitotic agents colchicine, combretastatin A4 and amphethinile
AUTHOR(S): McGown, A. T.; Fox, B. W.
CORPORATE SOURCE: Paterson Inst. Cancer Res., Christie Hosp., Withington/Manchester, M20 9BX, UK
SOURCE: Anti-Cancer Drug Design (1989), 3(4), 249-54
CODEN: ACDDEA; ISSN: 0266-9536
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The novel agents amphethinile and combretastatin A4 were very similar to colchicine in their interactions with purified tubulin. All 3 agents inhibited tubulin assembly at similar treatment levels and had comparable affinity consts. for tubulin. Amphethinile and combretastatin A4 were capable of displacing colchicine but not vinblastine from tubulin. A comparison of the structures of these agents showed that whereas colchicine and combretastatin A4 contain a trimethoxybenzene group (a moiety also found in other colchicine-like agents such as podophyllotoxins and steganacin) no obvious similarity was seen for amphethinile. The 3-dimensional structures of these agents, detd. from either crystallog. data or by energy minimization procedures, showed, however, that all 3 agents consist of 2 planar, or almost planar, ring systems which were tilted with respect to each other. Using computer graphic techniques it was shown that their ring system were superimposable and that the planar sections of each mol. were at an angle of 50-60.degree. to each other. Thus the angular bicyclic structure of these agents is one detg. factor for their efficient binding to tubulin.
IT **117048-59-6**, NSC 817373
RL: BIOL (Biological study)
(tubulin assembly inhibition by, structure in relation to)
RN 117048-59-6 CAPLUS
CN Phenol, 2-methoxy-5-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



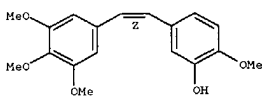
L24 ANSWER 153 OF 157 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1989:400276 CAPLUS
DOCUMENT NUMBER: 111:276
TITLE: Isolation and structure of the strong cell growth and tubulin inhibitor combretastatin A-4
AUTHOR(S): Pettit, G. R.; Singh, S. B.; Hamel, E.; Lin, C. M.; Alberts, D. S.; Garcia-Kendall, D.
CORPORATE SOURCE: Cancer Res. Inst., Arizona State Univ., Tempe, AZ, 85287, USA
SOURCE: Experientia (1989), 45(2), 209-11
CODEN: EXPEAM; ISSN: 0014-4754
DOCUMENT TYPE: Journal
LANGUAGE: English
GI



I, Z
II, E, R2=Me

AB From Combretum caffrum were isolated combretastatin A-4 (I, R1 = R2 = Me, R3 = H), combretastatin A-5 (I, R1 = H, R2 = R3 = Me), and combretastatin A-6 (II, R1 = H and R3 = Me) (the latter as the silyl ether). The structures of these compds. detd. by spectroscopic methods were confirmed by total syntheses. Combretastatins A-4, A-5 and A-6 were significantly active against murine L1210 and P388 lymphocytic leukemia cell lines with esp., combretastatin A-4 competing with combretastatin A-1 as the most inhibitor of colchicine binding to tubulin yet described. Combretastatin A-4 was an inhibitor of tubulin polymn.
IT **117048-59-6**, Combretastatin A-4
RL: RCT (Reactant); RACT (Reactant or reagent)
(of Combretum caffrum, as tubulin and neoplasm inhibitors, structure and synthesis of)
RN 117048-59-6 CAPLUS
CN Phenol, 2-methoxy-5-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

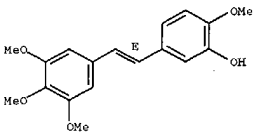
Double bond geometry as shown.



IT **117048-62-1**
RL: BIOL (Biological study)
(of Combretum caffrum, structure of)
RN 117048-62-1 CAPLUS
CN Phenol, 2-methoxy-5-[(1E)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA

L24 ANSWER 153 OF 157 CAPLUS COPYRIGHT 2003 ACS (Continued)
INDEX NAME)

Double bond geometry as shown.

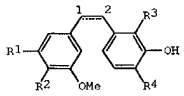


L24 ANSWER 154 OF 157 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1989:114573 CAPLUS
DOCUMENT NUMBER: 110:114573
TITLE: Isolation and synthesis of combretastatins as neoplasm inhibitors
INVENTOR(S): Pettit, George R.; Singh, Sheo Bux
PATENT ASSIGNEE(S): Arizona State University, USA
SOURCE: Eur. Pat. Appl., 31 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 276051	A2	19880727	EP 1988-300064	19880106
EP 276051	A3	19881130		
EP 276051	B1	19910821		
R: AT, BE, CH, DE, ES, FR, GB, GR, IT, LI, LU, NL, SE				
CA 1338645	A1	19961015	CA 1987-554733	19871217
JP 63233939	A2	19880929	JP 1987-327577	19871225
JP 2558131	B2	19961127		
AT 66452	E	19910915	AT 1988-300064	19880106
ES 2038747	T3	19930801	ES 1988-300064	19880106
US 5409953	A	19950425	US 1992-832998	19920210
US 5569796	A	19961029	US 1994-340156	19941115

PRIORITY APPLN. INFO.: US 1987-590 19870106
EP 1988-300064 19880106
US 1992-832998 19920210

OTHER SOURCE(S): MARPAT 110:114573
GI



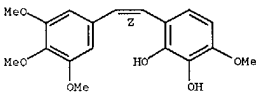
AB The title compds. (I; R1, R4 = OH, OMe; R2 = H, OMe; R3 = H, OH; R1R2 = OCH2O; 1,2-satd. or unsatd.) were synthesized and isolated from stem-wood of Combretum caffrum. 2,3,4-(HO)3C6H2CHO was added to aq. Na2B4O7 and, after 30 min stirring, NaOH and (MeO)2SO2 were added with stirring to give 2,3,4-(HO)2(MeO)C6H2CHO which was stirred 20 min with (Me3C)Me2SiCl in DMF contg. (Me2CH)2NEt to give 2,3,4-[(Me3C)Me2SiO]2(MeO)C6H2CHO. The latter was added to 3,4,5-(MeO)3C6H2CH2P+Ph3 Br- (prepn. given) previously treated with BuLi in THF to give, after deprotection, I (R1 = R2 = R4 = OMe, R3 = OH) (II) which had ID50 of 2 .mu.M for inhibition of microtubule assembly in vitro. Capsules were prepd. contg. II 200, starch 20, talc 20, and Mg stearate 2 g per thousand.

IT **109971-63-3P 119307-36-7P**
RL: RCT (Reactant); PREP (Preparation); RACT (Reactant or reagent)

L24 ANSWER 154 OF 157 CAPLUS COPYRIGHT 2003 ACS (Continued)
(isolation and synthesis of, as neoplasm inhibitor)

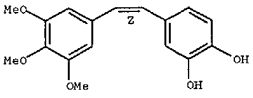
RN 109971-63-3 CAPLUS
CN 1,2-Benzenediol, 3-methoxy-6-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]-(9CI) (CA INDEX NAME)

Double bond geometry as shown.



RN 119307-36-7 CAPLUS
CN 1,2-Benzenediol, 4-[2-(3,4,5-trimethoxyphenyl)ethenyl]-, (Z)- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



L24 ANSWER 155 OF 157 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1989:68959 CAPLUS
DOCUMENT NUMBER: 110:68959
TITLE: Interactions of tubulin with potent natural and synthetic analogs of the antimitotic agent combretastatin: a structure-activity study
AUTHOR(S): Lin, Chii M.; Singh, Sheo B.; Chu, Ping S.; Dempcy, Robert O.; Schmidt, Jean M.; Pettit, George R.; Hamel, Ernest
CORPORATE SOURCE: Lab. Pharmacol. and Exp. Therap., Natl. Cancer Inst., Bethesda, MD, 20892, USA
SOURCE: Molecular Pharmacology (1988), 34(2), 200-8
CODEN: MOPMA3; ISSN: 0026-895X
DOCUMENT TYPE: Journal
LANGUAGE: English
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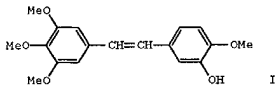
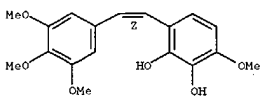


AB Available analogs (17 natural products and 22 synthetic agents) of combretastatin, an antineoplastic drug isolated from the bark of Combretum caffrum, were examd. for antimitotic and cytotoxic activity and for effects on tubulin polymn. and colchicine binding. Nineteen compds. inhibited cell growth by 50% or more at concns. of 1 .mu.M or less, and 14 inhibited tubulin polymn. by at least 50% at stoichiometric drug concns. The most potent cytotoxic agents strongly inhibited both tubulin polymn. and the binding of colchicine to tubulin. The most promising compd. is the (cis)-stilbene deriv. (cis)-1-(3,4,5-trimethoxyphenyl)-2-(3'-hydroxy-4'-methoxyphenyl)ethene (I), which has been named combretastatin A-4. This compd. inhibited cell growth by 50% at 7 nM, inhibited tubulin polymn. by 50% at 2.5 .mu.M (1/4 molar equivalent), and competitively inhibited colchicine binding with an apparent Ki of 0.14 .mu.M. The structure-activity relationship of these compds. is discussed.

IT **109971-63-3 117048-59-6 117048-62-1**
RL: PRP (Properties)
(antitumor and antimitotic and tubulin polymn.-inhibiting and colchicine binding-inhibiting effects of, structure in relation to)

RN 109971-63-3 CAPLUS
CN 1,2-Benzenediol, 3-methoxy-6-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]-(9CI) (CA INDEX NAME)

Double bond geometry as shown.



RN 117048-59-6 CAPLUS

=> log y

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	735.35	1189.14

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)	SINCE FILE ENTRY	TOTAL SESSION
CA SUBSCRIBER PRICE	-104.16	-106.11

STN INTERNATIONAL LOGOFF AT 08:28:42 ON 19 JUN 2003

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PASSWORD:
TERMINAL (ENTER 1, 2, 3, OR ?):2

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NEWS 1		Web Page URLs for STN Seminar Schedule - N. America
NEWS 2		"Ask CAS" for self-help around the clock
NEWS 3	Jun 03	New e-mail delivery for search results now available
NEWS 4	Aug 08	PHARMAMarketLetter(PHARMAML) - new on STN
NEWS 5	Aug 19	Aquatic Toxicity Information Retrieval (AQUIRE) now available on STN
NEWS 6	Aug 26	Sequence searching in REGISTRY enhanced
NEWS 7	Sep 03	JAPIO has been reloaded and enhanced
NEWS 8	Sep 16	Experimental properties added to the REGISTRY file
NEWS 9	Sep 16	CA Section Thesaurus available in CAPLUS and CA
NEWS 10	Oct 01	CASREACT Enriched with Reactions from 1907 to 1985
NEWS 11	Oct 24	BEILSTEIN adds new search fields
NEWS 12	Oct 24	Nutraceuticals International (NUTRACEUT) now available on STN
NEWS 13	Nov 18	DKILIT has been renamed APOLLIT
NEWS 14	Nov 25	More calculated properties added to REGISTRY
NEWS 15	Dec 04	CSA files on STN
NEWS 16	Dec 17	PCTFULL now covers WP/PCT Applications from 1978 to date
NEWS 17	Dec 17	TOXCENTER enhanced with additional content
NEWS 18	Dec 17	Adis Clinical Trials Insight now available on STN
NEWS 19	Jan 29	Simultaneous left and right truncation added to COMPENDEX, ENERGY, INSPEC
NEWS 20	Feb 13	CANCERLIT is no longer being updated
NEWS 21	Feb 24	METADEX enhancements
NEWS 22	Feb 24	PCTGEN now available on STN
NEWS 23	Feb 24	TEMA now available on STN
NEWS 24	Feb 26	NTIS now allows simultaneous left and right truncation
NEWS 25	Feb 26	PCTFULL now contains images
NEWS 26	Mar 04	SDI PACKAGE for monthly delivery of multifile SDI results
NEWS 27	Mar 20	EVENTLINE will be removed from STN
NEWS 28	Mar 24	PATDPAFULL now available on STN
NEWS 29	Mar 24	Additional information for trade-named substances without structures available in REGISTRY

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 NEWS 30  Apr 11  Display formats in DGENE enhanced
 NEWS 31  Apr 14  MEDLINE Reload
 NEWS 32  Apr 17  Polymer searching in REGISTRY enhanced
 NEWS 33  Jun 13  Indexing from 1947 to 1956 added to records in CA/CAPLUS
 NEWS 34  Apr 21  New current-awareness alert (SDI) frequency in
                  WPIDS/WPINDEX/WPIX
 NEWS 35  Apr 28  RDISCLOSURE now available on STN
 NEWS 36  May 05  Pharmacokinetic information and systematic chemical names
                  added to PHAR
 NEWS 37  May 15  MEDLINE file segment of TOXCENTER reloaded
 NEWS 38  May 15  Supporter information for ENCOMPPAT and ENCOMPLIT updated
 NEWS 39  May 16  CHEMREACT will be removed from STN
 NEWS 40  May 19  Simultaneous left and right truncation added to WSCA
 NEWS 41  May 19  RAPRA enhanced with new search field, simultaneous left and
                  right truncation
 NEWS 42  Jun 06  Simultaneous left and right truncation added to CBNB
 NEWS 43  Jun 06  PASCAL enhanced with additional data

 NEWS EXPRESS  April 4 CURRENT WINDOWS VERSION IS V6.01a, CURRENT
               MACINTOSH VERSION IS V6.0b(ENG) AND V6.0Jb(JP),
               AND CURRENT DISCOVER FILE IS DATED 01 APRIL 2003
 NEWS HOURS    STN Operating Hours Plus Help Desk Availability
 NEWS INTER    General Internet Information
 NEWS LOGIN    Welcome Banner and News Items
 NEWS PHONE    Direct Dial and Telecommunication Network Access to STN
 NEWS WWW      CAS World Wide Web Site (general information)

Enter NEWS followed by the item number or name to see news on that
specific topic.

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  research.  Use for software development or design or implementation
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  * * * * * * * * * * * * * * STN  Columbus  * * * * * * * * * * * * * * *

FILE 'HOME' ENTERED AT 08:43:45 ON 19 JUN 2003

=>
Uploading
THIS COMMAND NOT AVAILABLE IN THE CURRENT FILE
Do you want to switch to the Registry File?
Choice (Y/n):
Switching to the Registry File...
Some commands only work in certain files.  For example, the EXPAND
command can only be used to look at the index in a file which has an
index.  Enter "HELP COMMANDS" at an arrow prompt (=>) for a list of
commands which can be used in this file.

=> FILE REGISTRY

COST IN U.S. DOLLARS                          SINCE FILE      TOTAL
                                                 ENTRY    SESSION
FULL ESTIMATED COST                               0.42       0.42
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FILE 'REGISTRY' ENTERED AT 08:44:39 ON 19 JUN 2003

Property values tagged with IC are from the ZIC/VINITI data file provided by InfoChem.

STRUCTURE FILE UPDATES: 17 JUN 2003 HIGHEST RN 532924-24-6
DICTIONARY FILE UPDATES: 17 JUN 2003 HIGHEST RN 532924-24-6

TSCA INFORMATION NOW CURRENT THROUGH JANUARY 6, 2003

  Please note that search-term pricing does apply when
  conducting SmartSELECT searches.

Crossover limits have been increased. See HELP CROSSOVER for details.

Experimental and calculated property data are now available. See HELP PROPERTIES for more information. See STNote 27, Searching Properties in the CAS Registry File, for complete details:
http://www.cas.org/ONLINE/STN/STNOTES/stnotes27.pdf

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Uploading 10049248.str

L1   STRUCTURE UPLOADED

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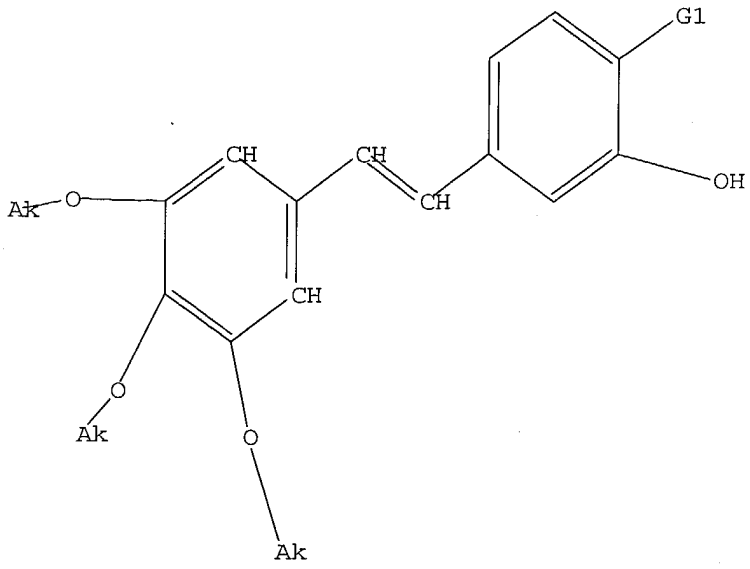
L1 HAS NO ANSWERS
L1   STR



G1 C,S,X

Structure attributes must be viewed using STN Express query preparation.

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=> s l1
SAMPLE SEARCH INITIATED 08:44:52 FILE 'REGISTRY'
SAMPLE SCREEN SEARCH COMPLETED -     22 TO ITERATE

100.0% PROCESSED      22 ITERATIONS                                 2 ANSWERS
SEARCH TIME: 00.00.01

FULL FILE PROJECTIONS:  ONLINE  **COMPLETE**
                        BATCH   **COMPLETE**
PROJECTED ITERATIONS:          159 TO      721
PROJECTED ANSWERS:               2 TO      124

L2             2 SEA SSS SAM L1

=> s l1 full
FULL SEARCH INITIATED 08:44:56 FILE 'REGISTRY'
FULL SCREEN SEARCH COMPLETED -    381 TO ITERATE

100.0% PROCESSED     381 ITERATIONS                                12 ANSWERS
SEARCH TIME: 00.00.01

L3            12 SEA SSS FUL L1

=> fil caplus
COST IN U.S. DOLLARS                                SINCE FILE      TOTAL
                                                       ENTRY    SESSION
FULL ESTIMATED COST                                   148.15     148.57

FILE 'CAPLUS' ENTERED AT 08:44:58 ON 19 JUN 2003
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FILE COVERS 1907 - 19 Jun 2003  VOL 138 ISS 25
FILE LAST UPDATED: 18 Jun 2003  (20030618/ED)

  This file contains CAS Registry Numbers for easy and accurate
  substance identification.


=> s l3
L4             6 L3

=> d ibib abs hitstr 1-6
```

L4 ANSWER 1 OF 6 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2002:487508 CAPLUS
DOCUMENT NUMBER: 137:47052
TITLE: Preparation of substituted stilbenes as antitumor agents
INVENTOR(S): Hadfield, John Anthony; McGown, Alan Thomson; Mayalarp, Stephen Patrick; Land, Edward John; Hamblett, Ian; Gaukroger, Keira; Lawrence, Nicholas James; Hepworth, Lucy Annette; Butler, John
PATENT ASSIGNEE(S): Cancer Research Ventures Limited, UK
SOURCE: PCT Int. Appl., 76 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002050007	A2	20020627	WO 2001-GB5702	20011220
WO 2002050007	A3	20021017		

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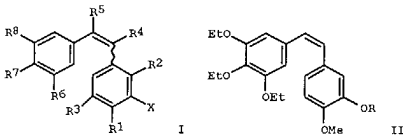
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

AU 2002016228	A5	20020701	AU 2002-16228		20011220
PRIORITY APPLN. INFO.:			GB 2000-31262	A	20001221
			GB 2001-295	A	20010105
			WO 2001-GB5702	W	20011220

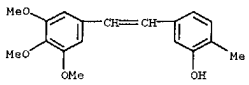
OTHER SOURCE(S): MARPAT 137:47052
GI



AB Stilbene and quinone compds. related to combretastatin A-4, such as I [X = OH, NO2, amino, aryl, heteroaryl, alkyl, alkoxy, CHO, halogen, haloalkyl, CONH2, O-aryl, O-heteroaryl; R1 = alkyl, CHO, alkoxy, amino, SR, CF3, halogen; R2, R3 = H, alkyl, alkoxy, OH, amino, thio, CF3, halogen; R4, R5 = H, alkyl, CH2NHCOR, CH2CONHR; R6, R7, R8 = H, alkyl, alkoxy; zigzag bond = cis-bond or trans-bond], or a salt or deriv. thereof, were prepd. for their use as anticancer compds. and prodrugs. The present invention further relates to the photochem. release of an active form of the compd. from a prodrug conjugate and the photochem. isomerization from a trans to cis form of I. Thus, reaction between 3,4,5-triethoxybenzyltriphenylphosphonium bromide and 3-O-t-butyldimethylsilyl-4-methoxybenzaldehyde yielded cis-stilbene [II; R = TBDMS] which upon desilylation afforded stilbene deriv. II [R = H (III)]. III showed IC50 = 0.018 .mu.M against MTT(K562) cell line.

IT **438534-68-0P**
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of substituted stilbenes as antitumor agents)

RN 438534-68-0 CAPLUS
CN Phenol, 2-methyl-5-[2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)



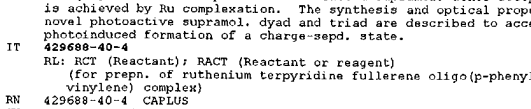
L4 ANSWER 2 OF 6 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2002:81725 CAPLUS
DOCUMENT NUMBER: 136:410547
TITLE: Metallo-supramolecular oligo(p-phenylene vinylene)/[60]fullerene architectures: towards functional materials
AUTHOR(S): El-Ghayoury, Abdelkrim; Schenning, Albertus P. H. J.; van Hal, Paul A.; Weidl, Christian H.; van Dongen, Joost L. J.; Janssen, Rene A. J.; Schubert, Ulrich S.; Meijer, E. W.
CORPORATE SOURCE: Laboratory of Macromolecular and Organic Chemistry, Eindhoven University of Technology, Eindhoven, 5600 MB, Neth.
SOURCE: Thin Solid Films (2002), 403-404, 97-101
CODEN: THSFAP; ISSN: 0040-6090
PUBLISHER: Elsevier Science S.A.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The assembly of .pi.-conjugated [oligo(p-phenylene vinylene)] (OPV) donors and [60]fullerene acceptor moieties into a supramol. donor-acceptor system is achieved by Ru complexation. The synthesis and optical properties of a novel photoactive supramol. dyad and triad are described to access the photoinduced formation of a charge-sepd. state.

IT **429688-40-4**
RL: RCT (Reactant); RACT (Reactant or reagent)
(for prepn. of ruthenium terpyridine fullerene oligo(p-phenylene vinylene) complex)

RN 429688-40-4 CAPLUS
CN 1,4-Benzenediol, 2-[2-[2,5-dihydroxy-4-[2-[3,4,5-tris(dodecyloxy)phenyl]ethenyl]phenyl]ethenyl]-5-[2-(4-ethynyl-2,5-dihydroxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

PAGE 1-A



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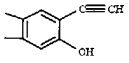

IT **429688-35-7DP**, substituted
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(for prepn. of ruthenium terpyridine fullerene oligo(p-phenylene vinylene) complex)

RN 429688-35-7 CAPLUS
CN 1,4-Benzenediol, 2-[2-[2,5-dihydroxy-4-([2,2':6',2''-terpyridin]-4'-

L4 ANSWER 1 OF 6 CAPLUS COPYRIGHT 2003 ACS (Continued)
= cis-bond or trans-bond], or a salt or deriv. thereof, were prepd. for their use as anticancer compds. and prodrugs. The present invention further relates to the photochem. release of an active form of the compd. from a prodrug conjugate and the photochem. isomerization from a trans to cis form of I. Thus, reaction between 3,4,5-triethoxybenzyltriphenylphosphonium bromide and 3-O-t-butyldimethylsilyl-4-methoxybenzaldehyde yielded cis-stilbene [II; R = TBDMS] which upon desilylation afforded stilbene deriv. II [R = H (III)]. III showed IC50 = 0.018 .mu.M against MTT(K562) cell line.

IT **438534-68-0P**
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of substituted stilbenes as antitumor agents)

RN 438534-68-0 CAPLUS
CN Phenol, 2-methyl-5-[2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

L4 ANSWER 2 OF 6 CAPLUS COPYRIGHT 2003 ACS (Continued)
ylethynyl)phenyl]ethenyl]-5-[2-[2,5-dihydroxy-4-[2-[3,4,5-tris(dodecyloxy)phenyl]ethenyl]phenyl]ethenyl]- (9CI) (CA INDEX NAME)

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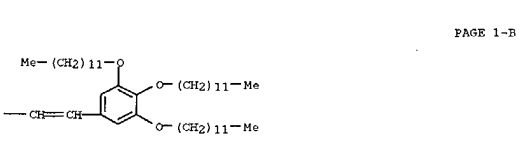

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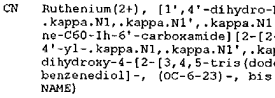


IT **429688-39-1DP**, substituted
RL: PRP (Properties); SPN (Synthetic preparation); PREP (Preparation)
(prepn. and photoinduced charge sepn. in ruthenium terpyridine fullerene oligo(p-phenylene vinylene) complex)

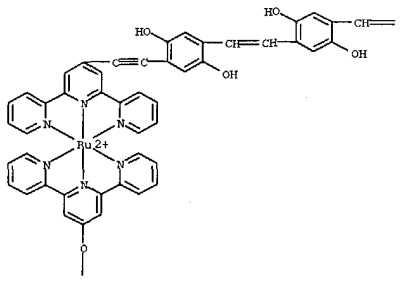
RN 429688-39-1 CAPLUS
CN Ruthenium(2+), [1',4'-dihydro-N-[5-[([2,2':6',2''-terpyridin]-4'-yl-.kappa.N1,.kappa.N1',.kappa.N1'')oxy]pentyl]naphtho[2',3':1,9][5,6]fullerene-C60-Ih-6'-carboxamide][2-[2-[2,5-dihydroxy-4-[([2,2':6',2''-terpyridin]-4'-yl-.kappa.N1,.kappa.N1',.kappa.N1'')ethynyl]phenyl]ethenyl]-5-[2-[2,5-dihydroxy-4-[2-[3,4,5-tris(dodecyloxy)phenyl]ethenyl]phenyl]ethenyl]-1,4-benzenediol]-, (OC-6-23)-, bis[tetrafluoroborate(1-)] (9CI) (CA INDEX NAME)

CM 1

CRN 429688-38-0
CMF C172 H133 N7 O11 Ru
CCI CCS

L4 ANSWER 2 OF 6 CAPLUS COPYRIGHT 2003 ACS (Continued)

PAGE 1-A



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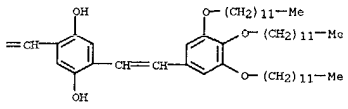

L4 ANSWER 2 OF 6 CAPLUS COPYRIGHT 2003 ACS (Continued)

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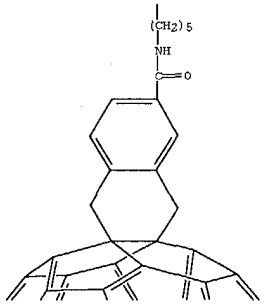

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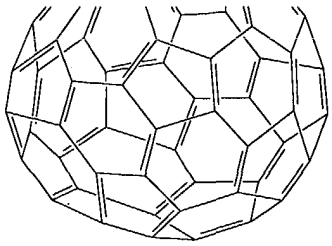


CM 2

CRN 14874-70-5
CMF B F4
CCI CCS

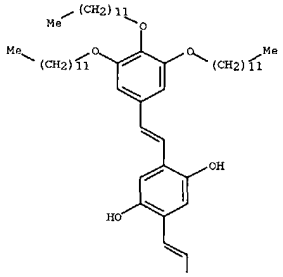
L4 ANSWER 2 OF 6 CAPLUS COPYRIGHT 2003 ACS (Continued)

IT **429688-37-9DP**, substituted
RL: SPN (Synthetic preparation); PREP (Preparation)
(prepn. of)
RN 429688-37-9 CAPLUS
CN Ruthenium(2+), bis[2-[2-[2,5-dihydroxy-4-[([2,2':6',2''-terpyridin]-4'-yl-.kappa.N1,.kappa.N1',.kappa.N1'')ethynyl]phenyl]ethenyl]-5-[2-[2,5-dihydroxy-4-[2-[3,4,5-tris(dodecyloxy)phenyl]ethenyl]phenyl]ethenyl]-1,4-benzenediol]-, (OC-6-1'2)-, bis[tetrafluoroborate(1-)] (9CI) (CA INDEX NAME)

CM 1

CRN 429688-36-8
CMF C166 H210 N6 O18 Ru
CCI CCS

PAGE 1-A



L4 ANSWER 2 OF 6 CAPLUS COPYRIGHT 2003 ACS (Continued)

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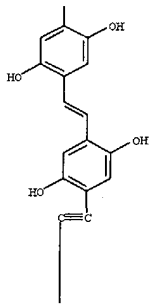

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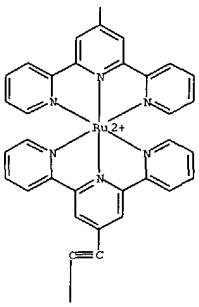
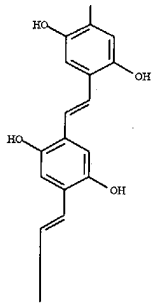


L4 ANSWER 2 OF 6 CAPLUS COPYRIGHT 2003 ACS (Continued)

PAGE 4-A



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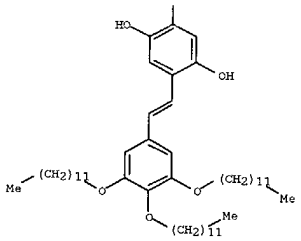

CM 2

CRN 14874-70-5
CMF B F4

L4 ANSWER 2 OF 6 CAPLUS COPYRIGHT 2003 ACS (Continued)
CCI CCS

REFERENCE COUNT: 33 THERE ARE 33 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 3 OF 6 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2001:137169 CAPLUS
DOCUMENT NUMBER: 134:178403
TITLE: Preparation and use of cis-stilbenes with vascular damaging activity
INVENTOR(S): Davis, Peter David
PATENT ASSIGNEE(S): Angiogene Pharmaceuticals Ltd., UK
SOURCE: PCT Int. Appl., 17 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001012579	A2	20010222	WO 2000-GB3067	20000809
WO 2001012579	A3	20011011		
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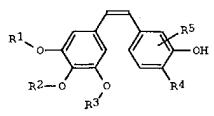
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
EP 1206429	A2	20020522	EP 2000-951727	20000809
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL				
JP 2003507356	T2	20030225	JP 2001-516880	20000809

PRIORITY APPLN. INFO.: GB 1999-18912 A 19990812
WO 2000-GB3067 W 20000809

OTHER SOURCE(S): MARPAT 134:178403
GI



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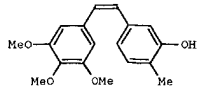


II

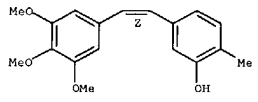
AB Compds. of formula I [wherein; R1, R2 and R3 are alkyl; R4 is (un)substituted alkyl, alkylthio, alkylsulfinyl, alkylsulfonyl, or halo;

L4 ANSWER 3 OF 6 CAPLUS COPYRIGHT 2003 ACS (Continued)
R5 is H, alkoxy, alkyl, alkylthio, hydroxy or halo] are prepd. Five examples are disclosed, one of which is a dihydrogen phosphate ester prodrug. The precursor of example II was prepd. by Wittig olefination of 3,4,5-trimethoxybenzyltriphenylphosphonium bromide and 3-tert-butyldimethylsilyloxy-4-methylbenzaldehyde. Fluoride-mediated deprotection of the silyloxy intermediate provided II as a white solid. Compds. I showed activity against tumor vasculature measured by redn. in functional vascular vol. in a mouse tumor assay (CaNT tumor-bearing mice). These compds. exhibit vascular damaging activity and are therefore potentially of value in treatment of diseases where reversal of neovascularization may have therapeutic benefit.

IT **288585-59-1P**, (Z)-1-(3-Hydroxy-4-methylphenyl)-2-(3,4,5-trimethoxyphenyl)ethene
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(prepn. and use of stilbenes with vascular damaging activity)

RN 288585-59-1 CAPLUS
CN Phenol, 2-methyl-5-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

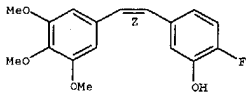
Double bond geometry as shown.



IT **326850-81-1P**, (Z)-1-(4-Fluoro-3-hydroxyphenyl)-2-(3,4,5-trimethoxyphenyl)ethene **326850-82-2P**, (Z)-1-(4-Chloro-3-hydroxyphenyl)-2-(3,4,5-trimethoxyphenyl)ethene **326850-83-3P**, (Z)-1-(4-Ethyl-3-hydroxyphenyl)-2-(3,4,5-trimethoxyphenyl)ethene
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. and use of stilbenes with vascular damaging activity)

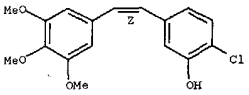
RN 326850-81-1 CAPLUS
CN Phenol, 2-fluoro-5-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



RN 326850-82-2 CAPLUS
CN Phenol, 2-chloro-5-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

L4 ANSWER 3 OF 6 CAPLUS COPYRIGHT 2003 ACS (Continued)
Double bond geometry as shown.



RN 326850-83-3 CAPLUS
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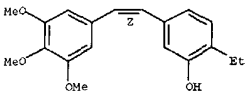
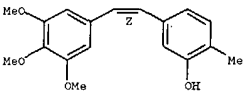
Double bond geometry as shown.



L4 ANSWER 4 OF 6 CAPLUS COPYRIGHT 2003 ACS (Continued)



REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 4 OF 6 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2000:592548 CAPLUS
DOCUMENT NUMBER: 133:177486
TITLE: Preparation of substituted stilbene compounds with vascular damaging activity
INVENTOR(S): Davis, Peter David
PATENT ASSIGNEE(S): Angiogene Pharmaceuticals Ltd., UK
SOURCE: PCT Int. Appl., 31 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000048590	A1	20000824	WO 2000-GB503	20000215
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
EP 1154767	A1	20011121	EP 2000-903824	20000215
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
JP 2002537250	T2	20021105	JP 2000-599382	20000215

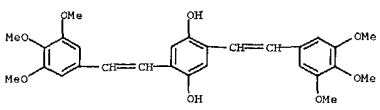
PRIORITY APPLN. INFO.: GB 1999-3403 A 19990216
WO 2000-GB503 W 20000215
OTHER SOURCE(S): MARPAT 133:177486
AB A vascular damaging agent AXB (A = substituted cis-stilbene; X = linker bond, atom, or group; B = moiety derived from an inhibitor of the formation or action of NO in mammalian systems), is claimed. Thus, (Z)-1-{3-(N-.alpha.-tert-butoxycarbonyl-N-.omega.-nitroarginyloxy)-4-methoxyphenyl}-2-(3,4,5-trimethoxyphenyl)ethene was stirred with CF3CO2H in CH2Cl2 to give (Z)-1-(4-methoxy-3-NG-nitroarginyloxyphenyl)-2-(3,4,5-trimethoxyphenyl)ethene. The latter at 50 mg/kg i.p. in mice bearing CaNT or SaS tumors gave 95% redn. in vascular vol. and 91-100% tumor necrosis.
IT **288585-59-1P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(prepn. of substituted stilbene compds. with vascular damaging activity)
RN 288585-59-1 CAPLUS
CN Phenol, 2-methyl-5-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

Double bond geometry as shown.

L4 ANSWER 5 OF 6 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2000:351266 CAPLUS
DOCUMENT NUMBER: 132:345122
TITLE: Sensor comprising an oligomer binding layer and method of making such sensor and arrays of such sensors
INVENTOR(S): Huyberechts, Guido; Jordens, Sven
PATENT ASSIGNEE(S): Interuniversitair Micro-Elektronica Centrum Vzw, Belg.; Universitaire Instituut Antwerpen
SOURCE: Eur. Pat. Appl., 18 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 1003033	A1	20000524	EP 1999-870236	19991116
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
EP 1003032	A1	20000524	EP 1998-870254	19981117
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				

PRIORITY APPLN. INFO.: EP 1998-870254 A 19981117
US 1999-122211P P 19990301
AB An aim of the invention is to provide a new type of sensor, capable of recognizing and/or quantifying analytes in a fluid. A further aim of the present invention is to provide such sensors with an oligomer material as a binding layer. A further aim of the present invention is to provide a novel method for the manuf. of such sensor wherein the oligomer layer is locally deposited on the sites of the sensor having a multitude of sensing sites. A biomol. recognizing an analyte is bound to the oligomer.
IT **270069-97-1DP**, alkyl derivs.
RL: ARG (Analytical reagent use); DEV (Device component use); RCT (Reactant); SPN (Synthetic preparation); ANST (Analytical study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(as oligomer; sensor comprising oligomer binding layer and method of making such sensor and arrays of such sensors)
RN 270069-97-1 CAPLUS
CN 1,4-Benzenediol, 2,5-bis[2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 7 THERE ARE 7 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 6 OF 6 CAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 2000:351265 CAPLUS
DOCUMENT NUMBER: 132:345121
TITLE: Sensor comprising an oligomer binding layer and method of making such sensor and arrays of such sensors
INVENTOR(S): Huyberechts, Guido; Jordens, Sven
PATENT ASSIGNEE(S): Interuniversitair Micro-Elektronica Centrum Vzw, Belg.; Universitaire Instelling Antwerpen
SOURCE: Eur. Pat. Appl., 14 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

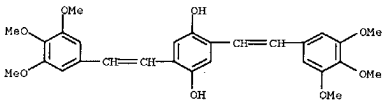
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 1003032	A1	20000524	EP 1998-870254	19981117
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
EP 1003033	A1	20000524	EP 1999-870236	19991116
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
US 2002048751	A1	20020425	US 1999-441118	19991117

PRIORITY APPLN. INFO.: EP 1998-870254 A 19981117
US 1999-122211P P 19990301

AB An aim of the invention is to provide a new type of sensor, capable of recognizing and/or quantifying analytes in a fluid. A further aim of the present invention is to provide such sensors with an oligomer material as a binding layer. A further aim of the present invention is to provide a novel method for the manuf. of such sensor wherein the oligomer layer is locally deposited on the sites of the sensor having a multitude of sensing sites. A biomol. recognizing an analyte is bound to the oligomer.

IT **270069-97-1DP**, alkyl derivs.
RL: ARG (Analytical reagent use); DEV (Device component use); RCT (Reactant); SPN (Synthetic preparation); ANST (Analytical study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(as oligomer; sensor comprising oligomer binding layer and method of making such sensor and arrays of such sensors)

RN 270069-97-1 CAPLUS
CN 1,4-Benzenediol, 2,5-bis[2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 7 THERE ARE 7 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 6 OF 6 CAPLUS COPYRIGHT 2003 ACS (Continued)

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COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	28.47	177.04

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)	SINCE FILE ENTRY	TOTAL SESSION
CA SUBSCRIBER PRICE	-3.91	-3.91

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